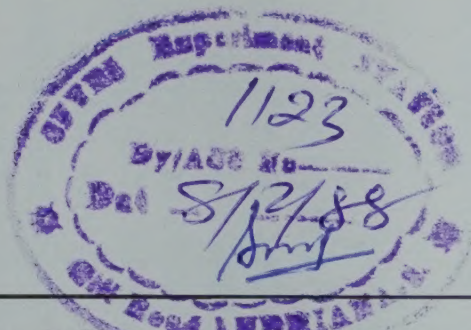


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## Communications

### A Novel Synthesis of 8-Allyl-7-methoxycoumarins

R S MALI\*, ANITA R MANEKAR & S G TILVE

Garware Research Center, Department of Chemistry, University of Poona, Pune 411 007

Received 10 August 1987; accepted 19 October 1987

An efficient, one-step synthesis of 8-allyl-7-methoxycoumarins (**3**) is described starting from 2-allyloxy-4-methoxybenzaldehyde (**1**). In this method both Claisen rearrangement and Wittig reaction occur in tandem manner.

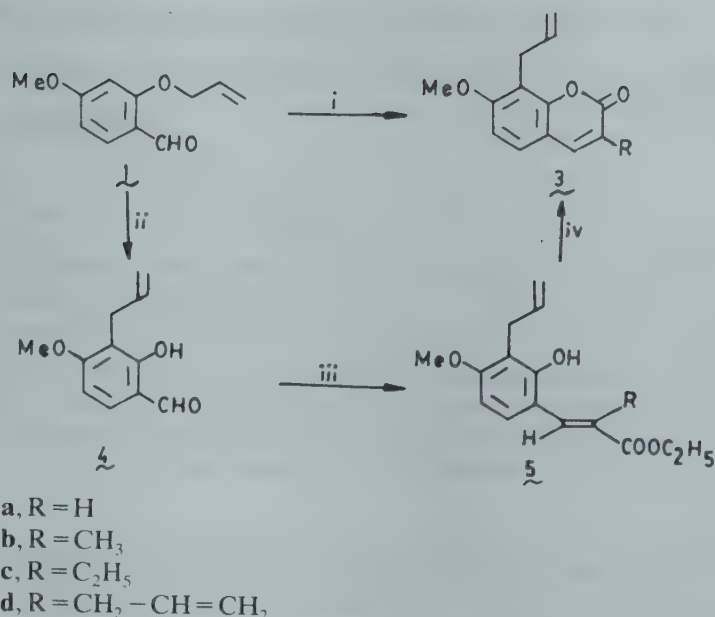
Two recent communications<sup>1,2</sup> report the preparation of 6-allyl-7-oxygenated coumarins, starting from preformed coumarins. Depending on the nature of the substituents 8-allyl-7-oxygenated coumarin is obtained either as a product or as a side product in these methods<sup>1,2</sup>. In all these Claisen rearrangements of this type of compounds<sup>1-4</sup>, two or more products are obtained. These results prompted us to report our one-pot method for the synthesis of 8-allyl-7-methoxycoumarins (**3**) starting from 2-allyloxy-4-methoxybenzaldehyde (**1**).

Allylation of 2-hydroxy-4-methoxybenzaldehyde (allyl bromide- $K_2CO_3$ -acetone method) led to **1**<sup>5</sup>, which on heating with phosphoranes<sup>6,7</sup> (**2a-d**) at 200° for 2-3 hr afforded 8-allyl-7-methoxycoumarins [(**3a**), 88%; (**3b**), 75%; (**3c**), 68%; (**3d**), 60%] (Scheme 1). These coumarins (**3a-d**) were fully characterised by their analytical, IR and PMR data.

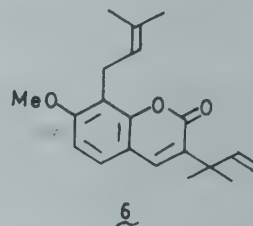
It is envisaged that conversion of **1** into **3** involves initial sigmatropic rearrangement of **1** to give **4** (*ortho*-Claisen rearrangement), which then reacts with phosphorane (**2**) to give hydroxy esters (**5**). Thermal cyclisation of **5** leads to **3**. As per our expectation heating **1** in dimethylaniline at 200-210°, exclusively led to **4** which was isolated and characterised. Compound **4** reacted with phosphoranes (**2a-d**) in THF solution to furnish the hydroxy esters (**5a-d**) in 61-85% yield. On thermal cyclisation, **5a-d** were converted into 8-allyl-7-methoxycoumarins (**3a-d**) in 62-84% yield.

The yields observed in the direct conversion of **1** into **3** via tandem Claisen rearrangement and Wittig reaction, are better than the three-step conversion of **1** into **3** via **4** and **5**.

The advantages of the present method are: (i) it is a one-step method; (ii) it gives a single product in the tandem Claisen rearrangement-Wittig reaction; (iii) substituent at 3-position can be varied,



Reagents: i,  $Ph_3P=C \begin{matrix} R \\ COOC_2H_5 \end{matrix}$  (**2**), heat; ii,  $PhNMe_2$ , 200-210°; iii, (**2**) THF r.t. (reflux for **5c**); iv, 180-190°/2-5 hr  
Scheme 1



e.g. it can provide natural coumarins, like ramosin-in<sup>8</sup> (**6**) in one-step; (iv) it makes use of stable phosphoranes and has wide applicability; and (v) it does not require preformed coumarins.

We thank Prof M S Wadia for helpful discussions. One of us (SGT) thanks the CSIR, New Delhi for the award of a junior research fellowship. Financial support from the CSIR, New Delhi, is also gratefully acknowledged.

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# Photochemical Transformations VI<sup>a</sup>: Organic Iodides (Part 5)—Templet Effect of Transition Metal Ions on Photocyclization of Some Olefinic Acyclic Terpene Iodides<sup>b,c</sup>

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Received 20 August 1987; accepted 25 September 1987

Photocyclization of citronellyl iodide in the presence of certain transition metal salts especially CuCl, results in a significant increase (from 16% to 35%) in the yield of the cyclization products. Similar results have been obtained with geranyl and neryl iodides (**11**, **17**). This enhancement of cyclization/elimination ratio is sought to be explained in terms of a templet effect of the transition metal ion.

The last one decade or so has seen much research activity in the area of transition metal catalysis in organic photochemistry<sup>1</sup>. Remarkably efficient intermolecular and intramolecular photocycloadditions of alkenes have been achieved in the presence of a Cu(I) catalyst. Many of these results have been rationalised in terms of Cu(I) participation as a bidentate chelating ligand<sup>1c,2</sup>. These results imply a sort of templet effect of metal ion in the photoreaction, and such catalysis should facilitate an intramolecular photocyclization, such as that of citronellyl iodide<sup>3</sup>, if such complexation can be visualised. The present work was carried out to evaluate such catalysis.

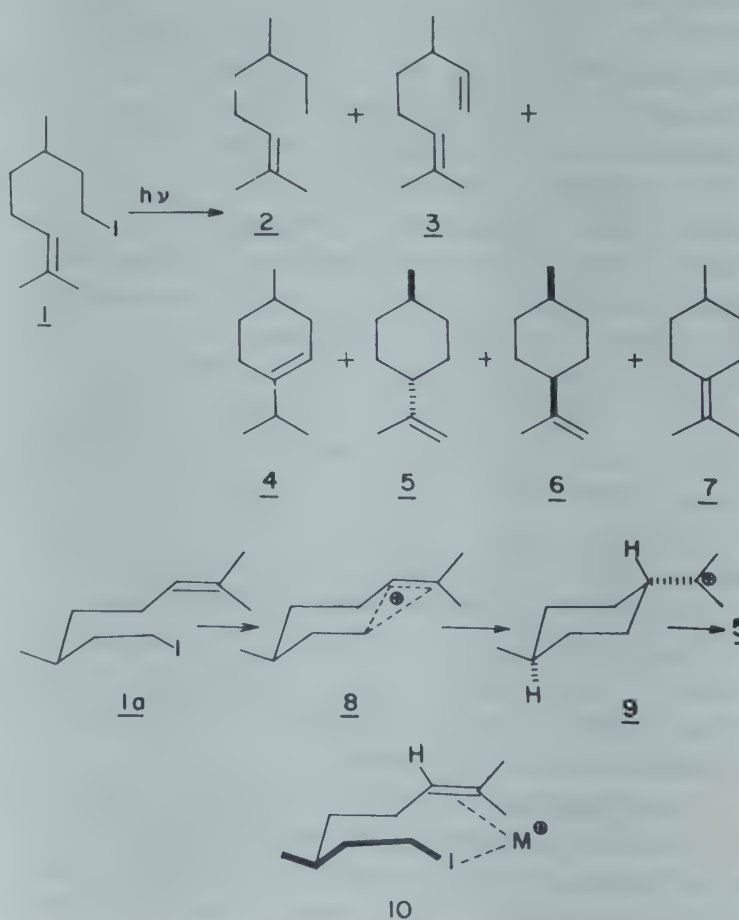
## Results

### Photocyclisation of citronellyl iodide (**1**)

Photocyclization of citronellyl iodide (**1**) and related compounds has been investigated in some detail and optimum reaction conditions delineated<sup>3</sup>. Under these experimental parameters (tetrahydrofuran as solvent, reaction temp.  $\sim 50^\circ$ ) citronellyl iodide yields, *inter alia*, cyclization products (**4**, **5**, **6**, **7**) in 54% yield, *trans*-menth-8-ene (**5**) being by far the major component. In view of this it was concluded that conformation **1a** of citronellyl iodide is important for the cyclization reaction, which then proceeds through **8** and **9** to give **5**. If this were so, then a metal ion with propensity for olefinic electron cloud and for iodide ion may serve to assist citronellyl iodide molecules

in folding into the required conformation by bidentate chelation of the type depicted in **10**. We are assured by the Frank-Condon principle<sup>4</sup> that this conformation will be reflected in the photo-reaction. Thus, this metal ion catalysis should enhance the cyclization to elimination ratio. This indeed has been found to be the case with some of the metal ions investigated.

Salts chosen for this particular study were the halides of Cu(I), Pd(II), Ag(I), Pt(II) and Hg(II), all known to complex with olefins to varying degrees<sup>5</sup>. Effect of these ions on a 1% solution of



(a)Part V: *Tetrahedron*, **43** (1987) 2543.

(b)MRC Communication No. 55

(c)Abstracted from the Ph.D. Thesis of K V Subbarao, M.S. University, Baroda (1983)

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Table 1—Photoirradiation of Citronellyl Iodide (**1**): Effect of Metal Ions<sup>a</sup>

No	Salt	Amount of salt (mg)	Product yield (%) <sup>c</sup>	Product composition (% GLC) <sup>b</sup> —[increasing GLC relative retention time]→							Total cyclization products (%)	Cyclization/elimination ratio
				2	3	Unknown	4	5	6	7		
1	None	—	74	9	27	8	2	36	7	10	55	2.03
2	CuCl	24.0	70	10	17	—	—	51	14	8	73	4.29
3	PdCl <sub>2</sub>	42.5	68	10	27	—	—	38	13	12	63	2.33
4	AgCl	35.0	70	11	31	—	—	40	12	6	58	1.87
5	PtCl <sub>2</sub>	64.0	68	14	31	—	—	37	10	8	55	1.77
6	HgCl <sub>2</sub>	65.2	77	19	18	—	—	41	12	10	63	3.50

<sup>a</sup> 2.7 g of citronellyl iodide in 270 ml THF containing molar equivalent of Et<sub>3</sub>N and  $2.44 \times 10^{-4}$  mol/litre of metal chloride; 400W medium pressure Hg vapour lamp; irradiation temp., ~ 50° (jacket water temp.).

<sup>b</sup> Column: 360 cm × 0.6 cm Al column, packed with 10% Carbowax 20M on 60-80 mesh Chromosorb W; temp., 100°; carrier gas, 60 ml H<sub>2</sub>/min.

<sup>c</sup> Total distilled product (% computed on the basis of elimination of H1).

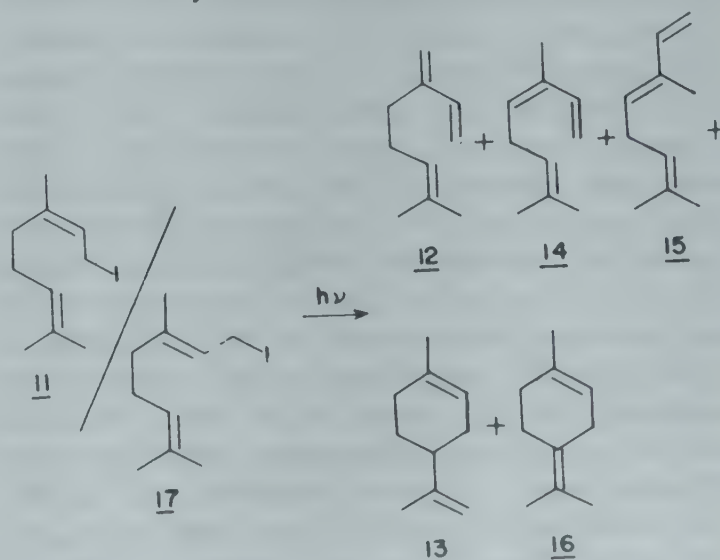
citronellyl iodide in tetrahydrofuran (THF) containing a molar equivalent of triethylamine (as H1 scavenger<sup>3</sup>), under irradiation, was investigated. All metal salts were used at a conc. of  $9.0 \times 10^{-4}$  mol/litre. This concentration was chosen keeping in view the solubility of the least soluble of the salts, namely AgCl, in the system. AgCl was found to have a solubility of 35 mg ( $2.44 \times 10^{-4}$  mol), at 30°, in 270 ml THF soln containing 2.70 g of citronellyl iodide and 1.02 g of Et<sub>3</sub>N. This corresponds to  $9.0 \times 10^{-4}$  M conc of AgCl in the system at 30°. Products of the reaction were identified by methods described earlier<sup>3b</sup>. Table 1 summarises the results of this study. From these data it is clear that leaving aside AgCl and PtCl<sub>2</sub>, which led to only marginal enhancement of total cyclization, the other three metal ions caused a distinct improvement in the percentage of total cyclization products. Of these, the effect of CuCl has been most profound, resulting in enhancement of the total cyclization products from 55% to 73%. This enhancement is essentially at the expense of elimination reaction†, the cyclization to elimination ratio having more than doubled in the case of CuCl. Both in the case of CuCl- and PdCl<sub>2</sub>-catalysed reactions, the amount of the reduction product, namely **2**, remained essentially unaltered, suggesting that these metal ions have practically no effect on the electron transfer process‡. However, it may be noted that in the case of HgCl<sub>2</sub> there is a signi-

ficant increase in the formation of the reduction product, from 9% to 19%.

#### Geranyl and neryl iodides

From the work described so far it is clear that certain metal salts, especially CuCl, are useful catalysts for photocyclization of citronellyl iodide. It was of obvious interest to extend this catalysis to other similar systems to ascertain the generality of this method.

Photocyclization of neryl iodide (**11**) in THF under the usual conditions to furnish, *inter alia*, dipentene (**13**) and terpinolene (**16**) has been described earlier<sup>7</sup>. The ratio of total cyclization to elimination was ~ 0.87. Now this reaction has been studied under CuCl catalysis using conditions developed for citronellyl iodide. For comparison, a non-catalysed reaction was also run. The products were identified as described earlier<sup>7</sup>. Table 2 summarises the results of this investigation, and it is clear from these that CuCl catalysis has again enhanced the cyclization reaction significantly. There



†The unknown in Table 1 is considered to be an isomerization product of **3** (to the more stable 2,6-dimethylocta-2,6-diene).

‡It has been earlier suggested<sup>3,6</sup> that in the case of alkyl and cycloalkyl iodides, photoirradiation leads to homolysis of carbon-iodine bond, followed by rapid electron transfer within the solvent-caged radical pair to generate an ion pair, from which product development essentially occurs.

Table 2—Photoirradiation of Neryl Iodide (**11**) and Geranyl Iodide (**17**): Effect of CuCl<sup>a</sup>

No	Substrate	Amt. of CuCl (mg)	Product yield (%) <sup>c</sup>	Product composition (% GLC) <sup>b</sup> —[Increasing GLC retention time]→							Total cyclization product (%)	Cyclization/elimination ratio
				Unidentified (4 components)	<b>12</b>	Unidentified	<b>13</b>	<b>14</b>	<b>15</b>	<b>16</b>		
1	Neryl iodide ( <b>11</b> )	0	65	28	30	1	23	4	4	10	33	0.87
2	Neryl iodide ( <b>11</b> )	20	60	22	11	3	26	—	16	22	48	1.78
3	Geranyl iodide ( <b>17</b> )	0	70	28	52	2	6	5	6	1	7	0.11
4	Geranyl iodide ( <b>17</b> )	20	67	15	29	4	10	3	27	12	22	0.37

<sup>(a)</sup> 2.20 g of the appropriate iodide in 220 ml THF containing molar equivalent of Et<sub>3</sub>N; reaction carried out with or without CuCl using conditions given under (a), Table 1.

<sup>(b,c)</sup> See footnotes to Table 1.

is almost a 50% increase in the yield of total cyclization products, and this enhancement is clearly at the expense of elimination.

When geranyl iodide (**17**) was used as the substrate<sup>7</sup> the cyclization to elimination ratio changed from 0.11 for the non-catalysed reaction to 0.37 for the CuCl-catalysed reaction (Table 2).

## Discussion

From the above results it is clear that certain metal ions facilitate the photocyclization reaction, and that the effect of CuCl is quite profound. A templet effect, wherein the reacting faces are held in the desired conformation through chelation with CuCl, was envisaged and the results obtained appear to bear this out. In the cyclization of geranyl iodide (**17**), which has its  $\Delta^6E$ -configured, isomerisation of this linkage to its *Z*-configuration at some stage, is a prerequisite before cyclisation. Cu(I)-catalysed photoisomerisation of olefins is well-documented<sup>1c</sup>. The fact that in the case of CuCl-catalysed photoreaction of both neryl iodide (**11**) and geranyl iodide (**17**) considerable quantities of *trans*- $\beta$ -ocimene (**15**) appear at the expense of its *cis*-isomer (**14**) and  $\beta$ -myrcene (**12**), is also consistent with such photoisomerizations. However, this difference in the product distribution could as well be due to the expected different nature of the transition state implicating CuCl catalysis. That this indeed is the case, when one considers significant enhancement in the formation of terpinolene (**16**) over dipentene (**13**) in the CuCl-catalysis. That this indeed is the case, when one considers significant enhancement in the formation of terpinolene (**16**) over dipentene (**13**) in the CuCl-catalysed photolysis of both neryl and geranyl iodides (Table 2), was established as follows. A

1% soln of dipentene (**13**) in THF containing one molar equivalent of Et<sub>3</sub>N and having  $9.0 \times 10^{-4}$  molar conc. of CuCl, was irradiated for 2 hr; no change in the starting **13** was observed. It is not possible to comment with any reasonableness about the nature of transition state implicating CuCl.

## Experimental Procedure

For general remarks see reference 7.

Preparations of citronellyl iodide<sup>3a</sup>, neryl iodide<sup>7</sup> and geranyl iodide<sup>7</sup> have been described previously.

Metal salts used were of reagent grade purity. Cuprous chloride was freshly prepared<sup>8</sup> everytime.

Tetrahydrofuran was refluxed over LAH and then distilled from it<sup>9</sup>. Triethylamine was refluxed over KOH pellets and then distilled over sodium<sup>10</sup>.

### General procedure for photoirradiation

Photoirradiation was carried out with Applied Photophysics medium-pressure Hg lamp 400 LQ (400 W), suspended in a double-walled, water-cooled, clear-fused quartz well, without filter. The substrate (0.01 mol) was used at 1% conc. in THF containing molar equivalent of Et<sub>3</sub>N and  $9.0 \times 10^{-4}$  molar conc. of the metal salt<sup>8</sup>. A steady stream of oxygen-free N<sub>2</sub> was passed through the

§For dissolving metal halides, following procedure was used: A mixture containing THF (50 ml), substrate (0.01 mol), Et<sub>3</sub>N (0.01 ml) and requisite quantity of the appropriate metal halide was stirred vigorously at room temp. ( $\sim 30^\circ$ ) for 5 min. It was diluted with (150 ml) and stirred till a clear soln was obtained ( $\sim 15$  min). This soln was transferred to the photoreactor and requisite additional quantity of THF added so as to make the final soln 1% with respect to the substrate.

soln for 1 min which was then irradiated; cool water was circulated through the reactor jacket at such a rate that irradiation could be carried out at 50°. The progress of the reaction was monitored by TLC (10% benzene in light petroleum). When the photostationary state had reached (2 hr), the solvent was carefully removed through an efficient Vigreux column. The product, so obtained, was passed through a short column of SiO<sub>2</sub>-gel/IIB<sup>11</sup> and eluted with light petroleum. The eluate was freed of solvent, as before, and the residue distilled *in vacuo* and the individual components identified by co-GLC with authentic samples<sup>3b,7</sup>. For GLC a Hewlett-Packard 5712A machine was used (for experimental parameters see footnote b, Table 1).

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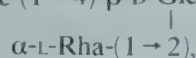
## Chemistry of Ayurvedic Crude Drugs: Part VI<sup>a</sup> – (Shatavari-1): Structure of Shatavarin-IV<sup>b,c</sup>

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The biological activity of *shatavari*, a reputed Ayurvedic crude drug, has been shown to reside in its alcohol extract, which has now been shown to consist of several steroidal glycosides. Isolation of four glycosides and the structure of one of these, namely, shatavarin-IV as  $\beta$ -D-Glc-(1 $\rightarrow$ 4)- $\beta$ -D-Glc-(1 $\rightarrow$ )-sarsasapogenin are described.



The Ayurvedic crude drug, *shatavari* of commerce comprises dried, decorticated roots of *Asparagus racemosus*<sup>1</sup> Willd. (fam: Liliaceae). Several therapeutic attributes have been mentioned in the classical ayurvedic literature for this drug, which has been specially recommended in cases of threatened abortion and as a galactagogue<sup>2</sup>. Preliminary pharmacological screening of various extracts of the crude drug appeared to confirm these claims<sup>3,4</sup>. Present work was undertaken to identify the active principle(s) responsible for anti-abortifacient activity.

After considerable experimentations involving biological screening of various extracts for antioxytocin activity<sup>3</sup>, a scheme finally emerged for the isolation of active fraction (vide Experimental). The alcohol extract, which, showed significant specific antioxytocin activity, on being partitioned between water and *n*-butanol, passed on the activity to the butanol phase. This fraction, which from its method of isolation was considered to be glycosidic in nature, was found to be a complex mixture of at least nine compounds (TLC) of which four could be obtained pure (in order of decreasing  $R_f$ ): compound A ( $R_f$  0.52, m.p. 152-154.5°), shatavarin-IV ( $R_f$  0.46, m.p. 307-309°), shatavarin-II ( $R_f$  0.28, m.p. 195-200°) and shatavarin-I ( $R_f$  0.24, m.p. 184-187°). Of these, only shatavarin-I showed specific antioxytocic activity, both *in vitro* and *in vivo*; the compound showed no progesta-

tional or esterogenic activity<sup>3b,3c,†</sup>. All three shatavarins yielded the same aglycone on acid hydrolysis and hence, structural investigations were first undertaken on shatavarin-IV, which is easier to isolate and purify<sup>‡</sup>.

### Shatavarin-IV

This compound analysed for C<sub>45</sub>H<sub>74</sub>O<sub>17</sub> and on permethylation (DMSO, NaH, MeI) gave a non-amethyl derivative (foam, m.p. 73-76°), and on peracetylation (Ac<sub>2</sub>O, pyr) a nonacetylated product (m.p. 128-131°). On acid hydrolysis (2N H<sub>2</sub>SO<sub>4</sub> aq. dioxane) shatavarin-IV furnished L-rhamnose and D-glucose (ratio, 1:2; paper chromatography, GLC of TMS derivatives), besides an aglycone, readily identified (m.p.,  $[\alpha]_D$ , TLC, IR, PMR, mass, and those of the derived acetate) as sarsasapogenin (**1**)<sup>5</sup>. In fact, isolation of **1** as a product of acid hydrolysis of alcohol extract of the defatted *shatavari* had been reported earlier<sup>6</sup>. The IR spectrum of shatavarin-IV displayed bands at 990, 925, 900 and 855 cm<sup>-1</sup> expected of a spirostanol<sup>7</sup>, indicating that the spirostanol structure is primary to the saponin and does not arise from a secondary cyclization of a furastanol during acid hydrolysis. Furthermore, since the 925 cm<sup>-1</sup> absorption is more intense than that at 900 cm<sup>-1</sup>, the chirality at C-25 is *s* in shatavarin-

<sup>a</sup>Part V, *Tetrahedron*, **38** (1982) 2949.

<sup>b</sup>NCL Communication No. 4316.

<sup>c</sup>Presented at First International Conference on Chemistry and Biotechnology of Biologically Active Natural Products, Varna, Bulgaria, Sept. 21-26, 1981.

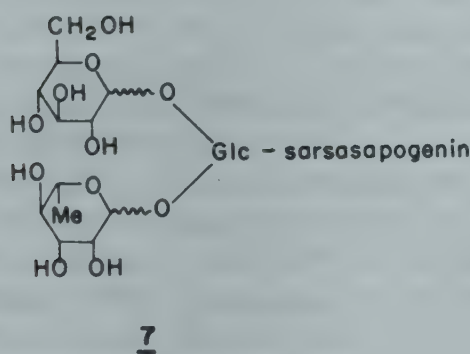
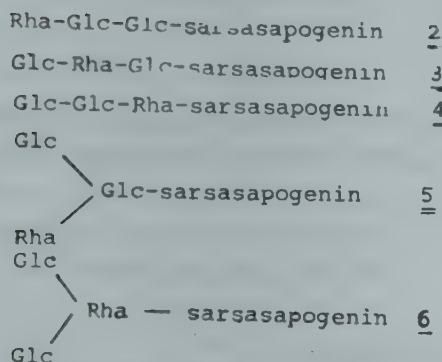
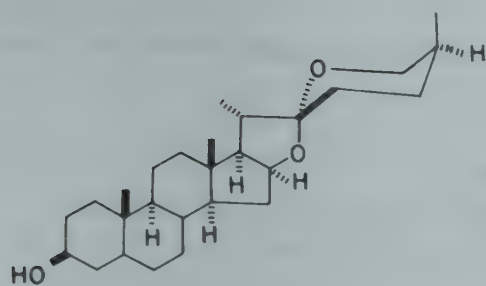
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<sup>e</sup>Present address: Xechem Inc., Rosemont, Ill., USA.

<sup>f</sup>Present address: Malti-Chem Research Centre, Nandesari, Vadodara.

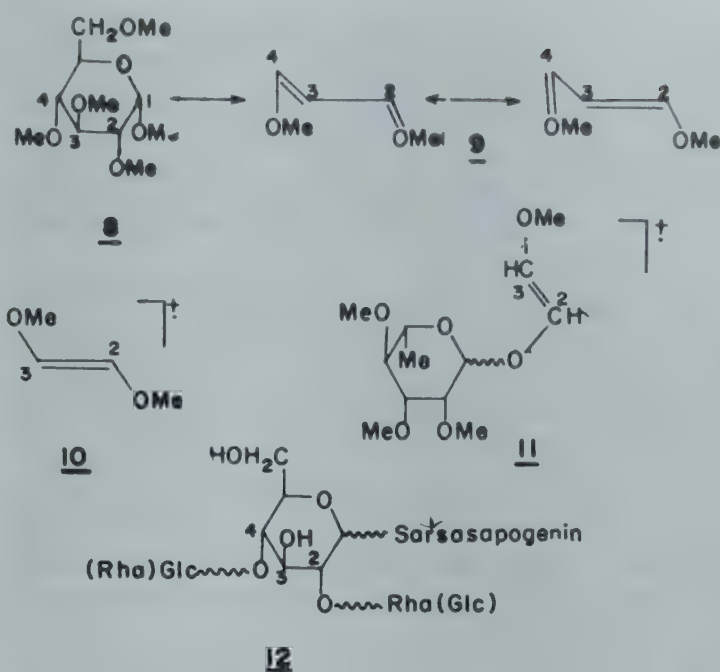
<sup>†</sup>In publications cited under refs. 1 and 3 the equivalence of compounds is as follows: Saponin A<sub>4</sub> (= shatavarin-I), saponin A<sub>7</sub> (= shatavarin-IV).

<sup>‡</sup>This work was carried out many years ago (PR Ravikumar, Ph.D. Thesis, Poona University, 1972) when several modern techniques of spectroscopy were not known. These modern techniques have been now exploited for elucidating the structures of other compounds described in the following communication. Shatavarin-IV of well-established structure served as a reference compound to evaluate the potential of newer techniques.



IV, as depicted for its genin (**1**)<sup>5b</sup>. If one ignores the point(s) of linkage on the component sugars, then we have five possible gross structures (**2** to **6**) for shatavarin-IV.

Mass spectrometry<sup>8</sup> proved most useful in narrowing down the structural possibilities and finally helped in arriving at the correct gross structure for shatavarin-IV. Mass spectrum of shatavarin-IV showed ions at  $m/z$  416 (9.2%) and 578 (1%) arising from H-transfer accompanied by cleavage of the glycosidic linkage. These ions correspond, respectively, to the aglycone ion and aglycone-glucose ion. This clearly indicates linking of sarsasapogenin with glucose, thus excluding possible structures **4** and **6**. The mass spectrum of nonamethylshatavarin-IV showed two sets of ions:  $\{m/z$  219(27%), 187(99%), 155 (9.5%)}, and  $\{m/z$  189(100%), 157(17%), 125(72%)}. In each group, the ions differ from each other by 32 units (loss of MeOH) and are consistent with both glucose (1st group) and rhamnose (2nd group) being the end units. These considerations, then clearly lead to the branched structure **5**, which may now be expressed as **7**.



Further refinement of structure **7** was made possible by examining the mass spectrum of nonamethylshatavarin-IV in an incisive and critical manner. From the work of Kochetkov and co-workers<sup>9</sup> on the electron impact induced fragmentation of permethylglucose (**8**) it is clear that the ion  $m/z$  101(47%) arises essentially from carbon atoms 2, 3 and 4 of glucose and this fragment has been formulated as **9**. Obviously, this fragmentation can be, possibly, exploited to detect if C-2/C-4 of the glucose moiety attached to sarsasapogenin carry any of the other two sugar units. The mass spectrum of nonamethylshatavarin-IV displayed an ion at  $m/z$  479 (7%), consistent with the presence of rhamnose and the second glucose units at these positions. This then leads to two possible structures depicted in **12** for shatavarin-IV. Again, the base peak in the mass spectrum of permethylglucose occurred at  $m/z$  88, to which the ion **10** carrying atoms 2 and 3 of glucose was shown to make ~80% contribution<sup>11</sup>. Since the mass spectrum of the permethylated derivative displayed an ion at  $m/z$  262(3%) (cf. **11**) and none at  $m/z$  292 (if glucose replaced rhamnose), C-2 of glucose moiety directly linked to aglycone must, therefore, carry rhamnose.

These conclusions drawn on the basis of electron impact induced mass fragmentation, received support from chemical degradative studies. Acid-catalysed methanolysis of nonamethylshatavarin-IV furnished a product which on the basis of TLC and GLC (vide Experimental) and mixed GLC with authentic samples was found to consist of methyl 2,3,4-tri-O-methylrhamnopyranoside (RRT=1.00, both anomers), methyl 2,3,4,6-tetra-O-methylglucopyranoside (RRT=1.92,  $\beta$ -anomer,

minor; RRT = 2.37,  $\alpha$ -anomer, major), and methyl 3,6-di-O-methylglucopyranoside (RRT = 2.85). The last component was isolated by column chromatography and identified by direct comparison (IR, PMR and Mass) with an authentic sample<sup>10</sup>. These results are fully consistent with structure **12** for shatavarin-IV.

To complete the structural description of shatavarin-IV, configuration at anomeric centres must be elucidated. This was achieved with the aid of PMR spectroscopy<sup>11</sup> and molecular rotation studies<sup>12</sup>. In the PMR spectrum of nonmethylshatavarin-IV ( $\text{CDCl}_3$ ) the three anomeric protons occur at  $\delta$  4.37 (*d*,  $J = 7$  Hz), 4.65 (*d*,  $J = 7$  Hz), and 4.98 (*bs*). These data, both chemical shift-wise and coupling-wise, are consistent with the conclusion that of the three sugar moieties two have their anomeric protons axial-axial coupled and are thus clearly  $\beta$ -linked (anomeric H axial), while in the third sugar the anomeric proton should be equatorial-equatorial or equatorial-axial coupled. Since in the preferred chair conformation of rhamnose the C-2 hydrogen is equatorial, the two  $\beta$ -linkages are clearly assignable to the two glucose (which has C-2 hydrogen axial) moieties. The third sugar rhamnose may be  $\alpha$ - or  $\beta$ -linked. This was readily clarified by reference to PMR spectra of authentic  $\alpha$ -methyl 2,3,4-tri-O-methyl-L-rhamnopyranoside ( $\delta$  C-1H, 4.73 ppm, *bs*), and  $\beta$ -methyl 2,3,4-tri-O-methyl-L-rhamnopyranoside ( $\delta$  C-1H, 4.25 ppm, *bs*). Since the observed  $\delta$  value of 4.98 ppm is closer to that for the  $\alpha$ -rhamnoside, the third sugar namely rhamnose must be  $\alpha$ -linked. This, then leads to structure **13** for shatavarin-IV. Molecular rotation studies further reinforce this structure. It is known<sup>12</sup> that the molecular rotation of a steroidal glycoside can be

Table 1—Calculated Molecular Rotation of Structure **13**

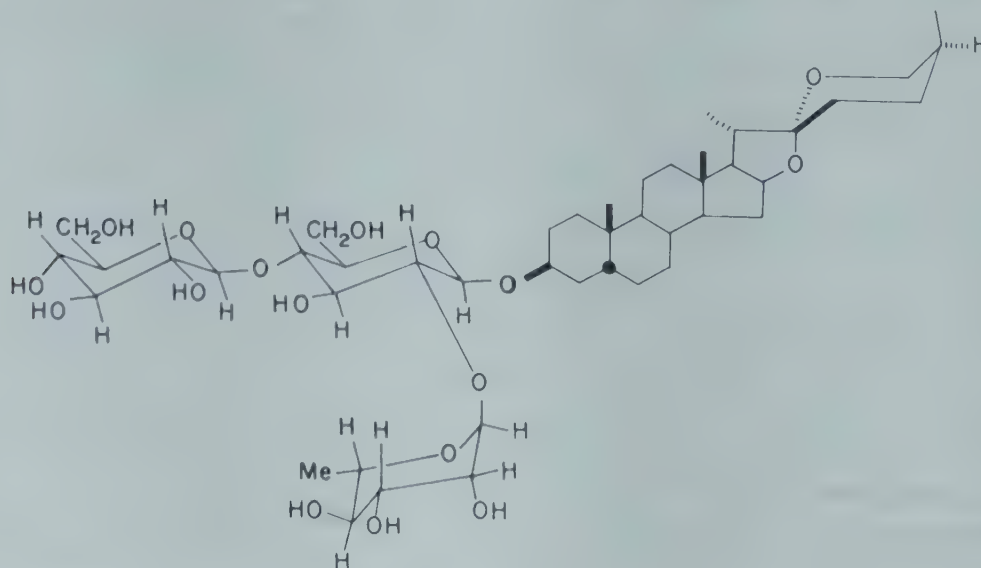
Component	$[\text{M}]_D^{25}$
Sarsasapogenin	$-322^\circ$
$\beta$ -Methyl D-glucopyranoside $\times 2^{12d}$	$-126^\circ$
$\alpha$ -Methyl L-rhamnopyranoside <sup>12d</sup>	$-111^\circ$
Total	$-559^\circ$

\*If rhamnose were  $\beta$ -linked, the calculated value would be:  $(-322^\circ) + (-126^\circ) + (+170^\circ)^{14d} = -378^\circ$

computed from the molecular rotation of the aglycone and each one of the sugar moieties. Thus, the calculated  $[\text{M}]_D$  value for structure **13** would be  $-559^\circ$  (Table 1), which is quite close to the observed value of  $-608^\circ$  for shatavarin-IV.

### Experimental Procedure

All m.ps and b.ps are uncorrected. Alumina for column chromatography ( $-80$ ,  $+250$  mesh) was treated with  $\text{HNO}_3$  aq<sup>13</sup>, washed neutral with water, dried, activated at  $\sim 450^\circ$  (5-6 hr), and standardized<sup>14</sup>. Silica gel for column chromatography ( $-100$ ,  $+200$  mesh) was washed with hot water till sulphate-free, dried, activated at  $125-130^\circ$  (6 hr) and standardized<sup>15</sup>. TLC was carried out on silica gel layers (0.3 mm) containing 15% gypsum; visualization of spots was done by spraying with 1% vanillin in 50%  $\text{H}_3\text{PO}_4$  aq followed by heating ( $\sim 100^\circ$ , 10 min). Paper chromatography (for sugars) was carried out on Whatman No. 1 paper by downward irrigation in the organic phase of *n*-BuOH-EtOH- $\text{H}_2\text{O}$  (4:1:4); visualization was done by spraying with satd  $\text{AgNO}_3$  aq, then with 10% ethanolic KOH, and finally washing the paper with 20%  $\text{Na}_2\text{S}_2\text{O}_3$  aq.

**13**

Following instruments were used for spectral/analytical data: Perkin-Elmer Polarimeter, model 141; Perkin-Elmer infracord, model 137E; Varian Associates A-60 spectrometer; CEC mass spectrometer, model 21-110B (70 eV, direct inlet system); Hewlett Packard 700 laboratory gas chromatograph or Aerograph model A-350-B. All PMR spectra were recorded with TMS as internal standard; signals are reported in ppm ( $\delta$ ).

#### *Plant material*

*Shatavari* was procured from Pune market and authenticated by the Pharmacognosy Unit, Indian Drugs Research Associated, Pune.

#### *Biological screening*

Screening of various extracts and pure compounds for antioxytocin activity was carried out by Prof. B.B. Gaitonde and his group at Grant Medical College (Dept of Pharmacology), Bombay<sup>3</sup>.

#### *Extraction and isolation of different glycosides*

*Shatavari* powder (4 kg) was extracted with hot acetone (13 litres  $\times$  2) in a Soxhlet-type apparatus for 48 hr each. The combined extract was freed of solvent to get a dark brown gum (104 g), which was devoid of the biological activity being sought, and hence was not investigated further. The marc was next similarly extracted with 95% EtOH (12 litres  $\times$  2) for 40 hr each to get, after solvent removal, a brown hygroscopic powder (265 g) with significant antioxytocin activity.

The alcohol extracted material (250 g) was dissolved in water (325 ml) and extracted with *n*-butanol satd with water (175 ml  $\times$  10). From the combined butanol phase, which carried the activity, solvent was removed to get a saponin mixture (typical foam test) as a brown foam (52.7 g). This material (60 g) was chromatographed on  $\text{Al}_2\text{O}_3/\text{IV}$  (1 kg; 6.5 cm  $\times$  29 cm) using *n*-BuOH satd with water as the loading solvent and eluent, to get the following six broad cuts, while monitoring with TLC (solvent:  $\text{CHCl}_3$  - MeOH -  $\text{H}_2\text{O}$ , 65:35:10; lower phase): Fraction 1: 200 ml  $\times$  4, 14.8 g, dark material; Fraction 2: 200 ml  $\times$  1, 1.2 g, major compound A ( $R_f$  0.52)\*\*; Fraction 3: 200 ml  $\times$  2, 3.8 g, major shatavarin-IV ( $R_f$  0.46); Fraction 4: 200 ml  $\times$  5, 18.3 g, shatavarin-I, -II and -III ( $R_f$  0.24, 0.28, 0.38 respectively); Fraction 5: 200 ml  $\times$  5, 9.1 g, shatavarin-I and sugars; and Fraction 6: 200 ml  $\times$  5, 2.3 g, sugars.

#### *Compound A* ( $R_f$ 0.52)

Fraction 2 was taken up in MeOH. On keeping the soln slowly deposited crystals, which were recrystallised from MeOH, m.p. 152-54.5°,  $[\alpha]_D$  -147.7° (MeOH, *c* 0.9%) (Found: C, 50.7; H, 8.6.  $\text{C}_{10}\text{H}_{20}\text{O}_6$  requires C, 50.8; H, 8.5).

#### *Shatavarin-IV* ( $R_f$ 0.46)

Fraction 3 (3.8 g) was rechromatographed on  $\text{Al}_2\text{O}_3/\text{II}$  (100 g; 3.3 cm  $\times$  11.0 cm) and eluted with *n*-BuOH satd with water. After rejecting the first (50 ml  $\times$  2) eluates, the main component was collected in the next eluates (50 ml  $\times$  6) as a brown foam (2.9 g). This material was leached with hot MeOH (5 ml) and the residue repeatedly crystallised from MeOH to get a white crystalline powder, m.p. 307-9°,  $[\alpha]_D$  -68.6° (pyridine, *c* 1.0%); IR (Nujol): 3500, 1220, 1135, 1100, 1080, 990, 925, 900, 855  $\text{cm}^{-1}$ , MS: *m/z* 578 ( $\text{M}^+$ -308, 1%), 416(9%), 399(7%), 183(13%), 181(20%), 163(8%), 147(11%), 145(8%), 139(100%), 129(5%), 121(16%) (Found: C, 60.9; H, 8.4.  $\text{C}_{45}\text{H}_{74}\text{O}_{17}$  requires C, 60.9; H, 8.4%).

#### *Shatavarin-II* ( $R_f$ 0.38) and *shatavarin-I* ( $R_f$ 0.28)

Fraction 4 (100 g) was rechromatographed ( $\text{Al}_2\text{O}_3/\text{II}$ , 2 kg, 7.6 cm  $\times$  49.5 cm; eluent, *n*-BuOH satd with water; 400-ml cuts) to get 67 g of enriched material. This was rechromatographed as before ( $\text{Al}_2\text{O}_3/\text{II}$ , 2 kg) to furnish a mixture (44.4 g) consisting essentially of shatavarin-I and -II. This product (5 g) was next chromatographed over  $\text{SiO}_2$  gel/IIA (2 kg, 7 cm  $\times$  101 cm) using lower phase from  $\text{CHCl}_3$ :  $\text{CH}_3\text{OH}$ :  $\text{H}_2\text{O}$  (65:35:10) mixture as the eluent. First 200 ml  $\times$  35 fractions gave shatavarin-II (0.538 g), followed by a mixture (200 ml  $\times$  5; 0.685 g). Next 200 ml  $\times$  11 fractions gave shatavarin-I (2.53 g).

Shatavarin-II, m.p. 195-200° (MeOH),  $[\alpha]_D$  -29.6° (MeOH, *c* 1.0%) (Found: C, 58.4; H, 8.5%).

Shatavarin-I, m.p. 184-87°,  $[\alpha]_D$  -34.2° (MeOH, *c* 1.0%). (Found: C, 55.6; H, 8.2%).

#### *Peracetylshatavarin-IV*

Shatavarin-IV (100 mg) in dry pyridine (6 ml) was mixed with acetic anhydride (6 ml) and the reaction mixture set aside at room temp. (25-30°) for 48 hr. Acetic anhydride and pyridine were removed at 70-85°/30 mm, and the residue worked up with  $\text{CHCl}_3$  in the usual manner to get a product (140 mg), which was purified by chromatography ( $\text{SiO}_2$  gel/IIA, 1.5 cm  $\times$  15 cm; 5 to 20% EtOAc in  $\text{C}_6\text{H}_6$ ) to get the required product (15% EtOAc in  $\text{C}_6\text{H}_6$ , 15 ml  $\times$  6) as a white powder (108 mg), m.p. 128-31°,  $[\alpha]_D$  -45.4° ( $\text{CHCl}_3$ , *c*

\*\*At 26°; solvent front 15 cm;  $R_f$  normalised to 10 cm solvent front.

1.1%); IR (nujol): 1765, 1250, 1045, 985, 910  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $2 \times \text{CMe}$  (3H, s, 0.75; 3H, s, 1.00),  $3 \times \text{CHMe}$  (signals not well-resolved:  $\sim 3\text{H}$ ,  $d$ , 1.00,  $J=6$  Hz;  $\sim 3\text{H}$ ,  $d$ , 1.08,  $J=6$  Hz;  $\sim 3\text{H}$ ,  $d$ , 1.21,  $J=5$  Hz),  $9 \times \text{OCOMe}$  ( $\sim 27\text{H}$ , overlapping singlets, spikes seen at 2.00, 2.08 and 2.13),  $\text{CHOAc}$  (complex overlapping multiplets, 3.3-5.2) (Found: C, 59.7; H, 7.6.  $\text{C}_{63}\text{H}_{92}\text{O}_{26}$  requires C, 59.8; H, 7.3%).

#### Permethylshatavarin-IV

Shatavarin-IV (1.0 g) was dissolved, at room temp ( $\sim 28^\circ$ ), in DMSO (25 ml; dried by distillation over  $\text{CaH}_2$ ) and to the stirred soln NaH (50% dispersion in paraffin, 0.7 g; worked with pet ether thrice before use) was added followed after 1/2 hr with MeI (10 ml), under cooling ( $\sim 20^\circ$ ). After stirring for another 1 hr at room temp, water (150 ml) was added and the product taken up in ether (60 ml  $\times 4$ ). The combined ether extract was washed with water (75 ml  $\times 4$ ), brine and dried ( $\text{Na}_2\text{SO}_4$ ). Solvent removal gave a product (1.05 g), which was remethylated as (as above) three times more to finally get a material (1 g) half of which was chromatographed over  $\text{SiO}_2$ -gel/IIA (1 cm  $\times 53$  cm). After rejecting the first eluates ( $\text{CHCl}_3$ , 20 ml  $\times 5$ ; 1% acetone in  $\text{CHCl}_3$ , 20 ml  $\times 2$ ), the required product (332 mg, white foam) was eluted with 1% acetone in  $\text{CHCl}_3$  (20 ml  $\times 5$ ). All attempts to crystallise the foam (m.p.  $73-76^\circ$ ) failed,  $[\alpha]_D -59.69^\circ$  ( $\text{CHCl}_3$ ,  $c$  0.97%); IR (Nujol): 1200-1000, 992, 922  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $2 \times \text{CMe}$  (3H, s, 0.77 ppm; 3H, s, 0.98 ppm),  $3 \times \text{CHMe}$  (signals not well-resolved  $\sim 3\text{H}$ ,  $d$ , 0.98;  $J=6\text{Hz}$ ;  $\sim 3\text{H}$ ,  $d$ , 1.08,  $J=6$  Hz;  $\sim 3\text{H}$ ,  $d$ , 1.28,  $J=6$  Hz),  $9 \times \text{OMe}$  (6H, s, 3.6; 9H, s, 3.5; 9H, s, 3.57; 3H, s, 3.60),  $\text{CHOR}$  (1H, unresolved, 4.35), anomeric  $H$  (1H,  $d$ , 4.37,  $J=7$  Hz; 1H,  $d$ , 4.65,  $J=7$  Hz; 1H,  $bs$ , 4.98); MS:  $m/z$  850 ( $M^+ -162$ , 0.2%), 479 (7%), 399, 262 (3%), 219 (27%), 189 (100%), 187 (99%), 157 (17%), 155 (9.5%), 125 (72%), 101 (33%), 95 (75%), 88 (47%), (Found: C, 64.3; H, 9.4.  $\text{C}_{54}\text{H}_{92}\text{O}_{17}$  requires C, 64.0; H, 9.2%).

#### Hydrolysis of shatavarin-IV

Shatavarin-IV (300 mg) in 2N  $\text{H}_2\text{SO}_4$  (60 ml) and dioxane (30 ml) was refluxed ( $\text{N}_2$ ) for 4 hr. The reaction mixture was cooled, diluted with  $\text{H}_2\text{O}$  (150 ml) and extracted with benzene (100 ml  $\times 3$ ). The benzene extract was washed with water (100 ml  $\times 4$ ), brine and dried ( $\text{Na}_2\text{SO}_4$ ). Solvent removal furnished a product (141 mg), which was purified by chromatography ( $\text{SiO}_2$  gel/IIA, 0.9 cm  $\times 26$  cm). 5% EtOAc in  $\text{C}_6\text{H}_6$  (12 ml  $\times 2$ )

eluted the required product (110 mg), which was repeatedly crystallized from MeOH-Et<sub>2</sub>O to get pure *sarsasapogenin* (62 mg), m.p.  $198-200^\circ$ ,  $[\alpha]_D -81^\circ$  ( $\text{CHCl}_3$ ,  $c$ , 0.8%) (lit.<sup>5</sup> m.p.  $200^\circ$ ;  $[\alpha]_D -78^\circ$ ,  $\text{CHCl}_3$ ); acetate ( $\text{Ac}_2\text{O}$  pyridine), m.p.  $147-48^\circ$ ,  $[\alpha]_D -70.1^\circ$  ( $\text{CHCl}_3$ ,  $c$  1.8%) (lit.<sup>7</sup> m.p.  $145^\circ$ ;  $[\alpha]_D -70^\circ$ ,  $\text{CHCl}_3$ ). Sarsasapogenin: IR (KBr): 3400, 1060, 987, 912, 890, 850  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ) spectrum was identical with that reported in literature<sup>16</sup>; mixed m.p. with an authentic sample was undepressed.

The aq. phase from the above work-up was neutralized by passing through a bed of anion exchange resin (IR-400,  $\text{OH}^-$  form; 150 ml), and then freed of water under suction to get the sugars (149 mg). Paper chromatography showed two spots identified by reference to authentic samples as glucose and rhamnose. Another portion (10 mg) of the total sugars was treated with dry pyridine (0.5 ml), trimethylsilyl chloride (0.2 ml) and hexamethyldisilazane (0.4 ml). The reaction mixture was shaken for 5 min and then freed of pyridine etc. ( $\sim 60^\circ$  under reduced pressure) and the residue in pet ether analysed by GLC<sup>17</sup> (6' column, 10% SE-30 on Chromosorb-W,  $190^\circ$ , 80 ml  $\text{H}_2/\text{min}$ ). For comparison purposes, authentic D-glucose and L-rhamnose in proportion of 2:1 were silylated and analyzed by GLC.

#### Methanolysis of permethylshatavarin-IV

Permethylshatavarin-IV (300 mg) was refluxed with 5% MeOH HCl (150 ml) for 5 hr. Methanol was removed under suction, dry methanol (50 ml) added and again removed as before. This product was used for TLC (solvent: 30% EtOAc in  $\text{C}_6\text{H}_6$ ; spray reagent, chlorosulphonic acid). Various components were identified by reference to authentic samples.

The rest of the material was treated with water (200 ml), filtered to remove aglycone, the filtrate neutralized by anion exchange resin (IR-400; 10 ml), and freed of water to get a residue (109 mg). A small sample was analyzed by GLC (6' column, 10% SE-30 on Chromosorb-W,  $135^\circ$ , 80 ml  $\text{H}_2/\text{min}$ ) and components identified by mixed GLC with authentic samples.

Rest of the product (100 mg) was chromatographed over  $\text{SiO}_2$ -gel/IIA (10 g, 1 cm  $\times 23$  cm).  $\text{CHCl}_3$  (25 ml  $\times 4$ ) eluted permethylglucose and permethylrhamnose; 42.4 mg). Next, 1% MeOH in  $\text{CHCl}_3$  (25 ml  $\times 4$ ) eluted (6.6 mg) a mixture (rejected). Finally, 5% MeOH, in  $\text{CHCl}_3$  (25 ml  $\times 5$ ) furnished 22.5 mg of a liquid identified (IR, PMR, Mass) as methyl 3,6-di-O-methylglucopyranoside.

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# A Convenient Strategy for Homologation of *p*-Oxygenated Benzaldehydes

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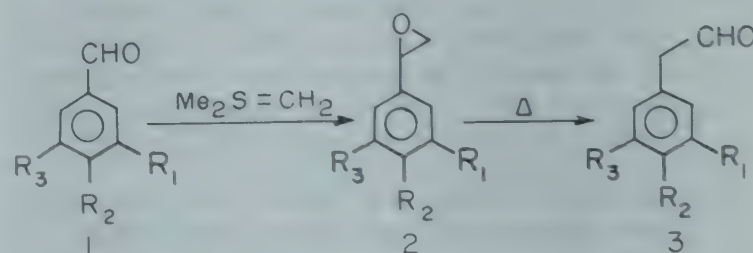
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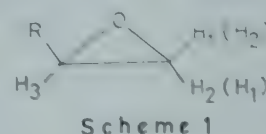
It is shown that *p*-oxygenated benzaldehydes can be conveniently obtained by pyrolysis of the corresponding oxiranes.

As part of an ongoing research we needed certain *p*-hydroxy/*p*-alkoxyphenylacetaldehydes and since known methods<sup>1-5</sup> failed to furnish acceptable yields, we developed a convenient and expeditious two-step sequence for their synthesis. This is described below.

The key reaction in this strategy (Scheme 1) is the regiospecific rearrangement of an 1,2-epoxyethylbenzene to the corresponding phenylacetaldehyde. In initial investigations Lewis acid-catalyzed<sup>6</sup> isomerization of the oxiranes was studied, but only polymeric materials resulted, possibly from rapid aldol condensation of the phenylacetyldehyde. Thermolysis<sup>7</sup>, on the other hand, furnished acceptable yields of the required aldehydes. Watson and Young<sup>8</sup> were the first to demonstrate that thermal isomerization of 1,2-epoxyethylbenzene (styrene epoxide) led to phenylacetaldehyde at 200-300°. A non-concerted free radical or ionic pathway was suggested. However, in our hands, heating of styrene epoxide (in a pyrex sealed tube) to 240-50° (5 min, 15 min) led to practically no reaction, while extended periods of heating (6 hr) resulted in much (~ 30%) polymerization, without an isolable production of phenylacetaldehyde†. Considering that in case of a *p*-hydroxylated or *p*-alkoxylated styrene epoxide, the oxirane ring-opening in the desired direction should be facilitated by an ionic pathway, we subjected *p*-methoxystyrene epoxide (**2a**) to thermal treatment (240°) for 5 min; the required *p*-methoxyphenylacetaldehyde (**3a**) could be isolated in ~ 65% yield. In contrast, the *m*-isomer (**2b**) failed to isomerize under the same conditions, though at higher temperature and under longer thermal exposure some 40% of the aldehyde (**3b**) was formed. This is consistent



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
a	H	OMe	H
b	OMe	H	H
c	OMe	OH	H
d	OMe	OTHP	H
e	OMe	OMe	H
f			H
g	OMe	OMe	OMe
h	H	H	H



Scheme 1

Table 1—Pyrolysis of 1,2-Epoxyethylbenzenes (**2**)

Epoxide	Reaction conditions		Phenylacetaldehyde( <b>3</b> ) (% yield)
	Temp. (°C)	Time (min)	
<b>2a</b>	240	5	<b>3a</b> (66%) <sup>a</sup>
<b>2b</b>	240	5	<sup>b</sup>
	250	15	<b>3b</b> (39%) <sup>c</sup>
<b>2d</b>	240	5	<b>3c</b> <sup>d</sup> (64%) <sup>a</sup>
<b>2e</b>	240	5	<b>3e</b> (66%) <sup>a</sup>
<b>2f</b>	240	5	<b>3f</b> (65%) <sup>a</sup>
<b>2g</b>	240	5	<b>3g</b> (65%) <sup>a</sup>
<b>2h</b>	240	5	<sup>b</sup>
	240	15	<sup>b</sup>
	240	360	<sup>e</sup>

(a) Balance is polymer

(b) 100% recovery of epoxide

(c) 39% recovery of epoxide; balance polymer

(d) During thermolysis OTHP group underwent cleavage to OH

(e) 70% recovery of epoxide; balance polymer

†Watson and Young<sup>8</sup> state: 'Substantial polymerization was observed upon thermolysis in sealed tubes at 200°, but rearrangement of 8:1 benzene or toluene solutions of styrene epoxide consistently provided yields of 91-96% of the aldehyde'. Pyrolysis of solutions was carried out in a stirred stainless steel reactor, and the reactor walls might have served to catalyze isomerization.

Table 2—1,2-Epoxyethylbenzenes (2)

Compound	b.p.°C/mmHg (m.p.)	Yield (%)	IR <sup>a</sup> (oxirane <sup>b</sup> , cm <sup>-1</sup> )	H <sub>1</sub> ( <i>m</i> )	H <sub>2</sub> ( <i>m</i> )	H <sub>3</sub> ( <i>dd</i> )	Found (reqd) %		Formula
							C	H	
<b>2a</b>	115-17°/1.2	96	810,840,930,1240	2.56	2.93	3.62	71.59(71.98)	6.66(6.71)	C <sub>9</sub> H <sub>10</sub> O <sub>2</sub>
<b>2b</b>	90-92/1	97	785,850,920,1240	2.55	2.92	3.65	71.62(71.98)	6.62(6.71)	C <sub>9</sub> H <sub>10</sub> O <sub>2</sub>
<b>2d</b>	136/0.75	94	820,840,950,1230	2.59	2.95	3.65	—	—	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>
<b>2e</b>	124/1.3	92	815,850,930,1240	2.56	2.95	3.64	66.35(66.65)	6.66(6.71)	C <sub>10</sub> H <sub>12</sub> O <sub>3</sub>
<b>2f</b>	106/1.5	95	810,850,940,1240	2.56	2.93	3.63	66.09(65.85)	5.28(4.91)	C <sub>9</sub> H <sub>8</sub> O <sub>3</sub>
<b>2g</b>	(51-52)	97	780,835,940,1240	2.56	2.94	3.63	63.24(62.84)	6.95(6.71)	C <sub>11</sub> H <sub>14</sub> O <sub>4</sub>

(a) Smear, except compound **2g** which was studied as nujol mull.

(b) Ref. 16

(c) Chemical shifts in  $\delta$ , ppm downfield from Me<sub>4</sub>Si; *m* = multiplet, *dd* = double doublet.

with an ionic pathway. The desired phenylacetaldehydes (**3c,3e,3f,3g**) were then prepared by this method of thermal isomerization (Table 1). All aldehydes listed therein are known compounds<sup>1,3,9,10</sup> and had been prepared earlier by other methods.

The oxiranes required for thermolytic studies were conveniently obtained by reaction of the appropriate benzaldehyde with methylenedimethylsulfurane<sup>11-13</sup>. For generation of the ylid, reaction of trimethylsulfonium methyl sulfate<sup>14</sup> with 60% NaOH aqueous proved convenient and expeditious, and its *in situ* reaction with the carbonyl compound was best carried out in the presence of a phase transfer catalyst<sup>14,15</sup>. Table 2 summarises important data concerning these epoxides, which are being reported for the first time.

### Experimental Procedure

IR spectra were taken as smears on a Perkin-Elmer model 781 infracord spectrophotometer and PMR spectra were recorded in CCl<sub>4</sub> solution on a Perkin-Elmer model R32 (90 MHz) spectrometer; chemical shifts are in  $\delta$ , ppm. GLC was carried out on a Hewlett-Packard 5712A gas chromatography (Al columns 180 cm  $\times$  0.3 cm; support, 60-80 mesh Chromosorb-W; carrier gas, H<sub>2</sub>; TC detector).

#### Preparation of oxiranes. General procedure

To freshly purified dimethyl sulfate (3.765 g, 0.029 mol) cooled to 0°, was introduced dimethyl sulphide (4.515 g, 0.072 mol) with stirring and cooling (0°). After stirring at 0° for 15 min, the reaction temperature was allowed to rise to 18-20° during 3 hr. To the crystalline megma thus obtained, were added benzene (10 ml), followed by 60% aq NaOH (7 ml, 0.11 mol) with stirring. After stirring for an additional few minutes, the appropriate aldehyde (0.026 mol) in benzene (20 ml), and 70% benzyltriethylammonium chloride aq (0.1 ml) were introduced. The reaction mixture was heated (50°) and stirred for 10 hr and then worked up in the usual

manner to get the required oxirane, which was purified by distillation. The product purity was > 98% by GLC (10% SE-30, temp. 150-200°).

#### Pyrolysis of oxiranes

Appropriate oxirane (**2g**) was sealed, along with a magnetic stirring needle in a pyrex ampule, under N<sub>2</sub>. This was rapidly immersed in bath preheated to 240°  $\pm$  1° and placed on a magnetic stirrer. After heating for appropriate period (Table 1), the ampule was withdrawn, cooled and the contents distilled to get the pure (GLC purity > 98%; 10% SE-30, temp. 150-200°) phenylacetaldehyde (Table 1).

Following aldehydes were thus obtained *p*-Methoxyphenylacetaldehyde<sup>11</sup> (**3a**), b.p. 110-15°/1 mm; IR: 1720, 1610, 1510, 1450, 1300, 1240, 1170, 1030, 830 cm<sup>-1</sup>; PMR: ArCH<sub>2</sub> (2H, *d*, 3.45), OMe (3H, *s*, 3.68), Ar-H (4H, *m*, 6.67-7.13), CHO (1H, *t*, 9.54). 4-Hydroxy-3-methoxyphenylacetaldehyde<sup>10</sup> (**3c**), b.p. 145-152°/2mm; IR: 3410, 1720, 1610, 1510, 1460, 1260, 1170, 1030, 820 cm<sup>-1</sup>; PMR: ArCH<sub>2</sub> (2H, *d*, 3.48), OMe (3H, *s*, 3.80), Ar-H (3H, *m*, 6.53-6.90), CHO (1H, *t*, 9.56). 3,4-Dimethoxyphenylacetaldehyde<sup>3</sup> (**3e**), b.p. 124-26°/0.3 mm; IR: 1720, 1595, 1520, 1460, 1260, 1150, 1030, 810 cm<sup>-1</sup>; PMR: ArCH<sub>2</sub> (2H, *d*, 3.45), OMe (6  $\times$  H, *s*, 3.75), Ar-H (3H, *m*, 6.5-6.8), CHO (1H, *t*, 9.52). 3,4-Methylenedioxyphenylacetaldehyde<sup>3</sup> (**3f**), b.p. 124-27°/2 mm; IR: 1720, 1610, 1500, 1445, 1360, 1240, 1190, 1040, 820 cm<sup>-1</sup>; PMR: ArCH<sub>2</sub> (2H, *d*, 3.45), methylenedioxy-H (2H, *s*, 5.89), Ar-H (3H, *m*, 6.4-6.8), CHO (1H, *t*, 9.54). 3,4,5-Trimethoxyphenylacetaldehyde<sup>1</sup> (**3g**), m.p. 40-41°; IR: 1720, 1595, 1520, 1460, 1260, 1150, 1030, 810 cm<sup>-1</sup>; PMR: ArCH<sub>2</sub> (2H, *d*, 3.45), 3  $\times$  OMe (3H, *s*, 3.69, 6H, *s*, 3.78), Ar-H (2H, *s*, 6.3), CHO (1H, *t*, 9.52).

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## Synthesis of a Distamycin Analogue: Tris(*m*-benzamido) Compound

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In order to understand the role of curvature of ligand in conformational and chemical specificity of DNA-drug [such as distamycin (Dst) and netropsin (Nt)] interactions a number of compounds have been synthesised. The synthetic strategy for one of the compounds in the series, tris(*m*-benzamido) compound, an analogue of Dst, which is essentially based on the route used by Bialer *et al.* [*Tetrahedron*, **34** (1978), 2239] for the synthesis of Dst with some modifications wherever necessary is reported.

The two oligopeptides, netropsin (Nt) and distamycin (Dst) bind specifically to the A<sub>T</sub>-rich regions of B-DNA via the minor groove<sup>1,2</sup> in a non-intercalative fashion. They also exhibit biological properties such as antibacterial, antiviral and anticancer activities. However, their clinical application is limited due to their cytotoxicity.

X-ray crystallographic evidence<sup>3,4</sup>, solution state investigations<sup>5-8</sup> coupled with theoretical model building studies have indicated that the bow-shaped structures with curved backbones of these molecules facilitate both the van der Waals contact and specific hydrogen bonds between the amides (on the concave side of the molecules) and the N-3 of adenine or the O-2 of thymine<sup>2,4,5,9</sup> in the minor groove of DNA. However, the role played by the curvature of the ligand in its interaction with DNA has not been fully understood. With an endeavour to comprehend the aspects of recognition between these drug molecules and DNA, we have taken up the synthesis of a series of analogues of Dst in our laboratory for the first time. However, in this communication, only the synthetic procedure adopted to obtain one such analogue, the tris(*m*-benzamido) compound is reported. This analogue constituted replacement of the N-methylpyrrole rings of Dst with three 1,3-disubstituted benzene rings and is referred to as the "trimer".

The trimer has a curvature greater than that of Dst. The physicochemical studies, such as UV and CD used to study the interaction between the trimer and DNA (natural and synthetic), however, have indicated lesser A-T preference of the trimer than Dst<sup>10</sup>.

In this paper, we report the synthesis and purification procedures used to obtain the trimer. The synthesis was accomplished essentially by the route used by Bialer *et al.*<sup>11</sup> for the synthesis of Dst with some modifications. These modifications were ne-

cessary at the intermediates (7), (10) and (11) because we obtained very low yields and a number of side products in DCC coupling step and Pinner reaction.

### Synthesis and purification

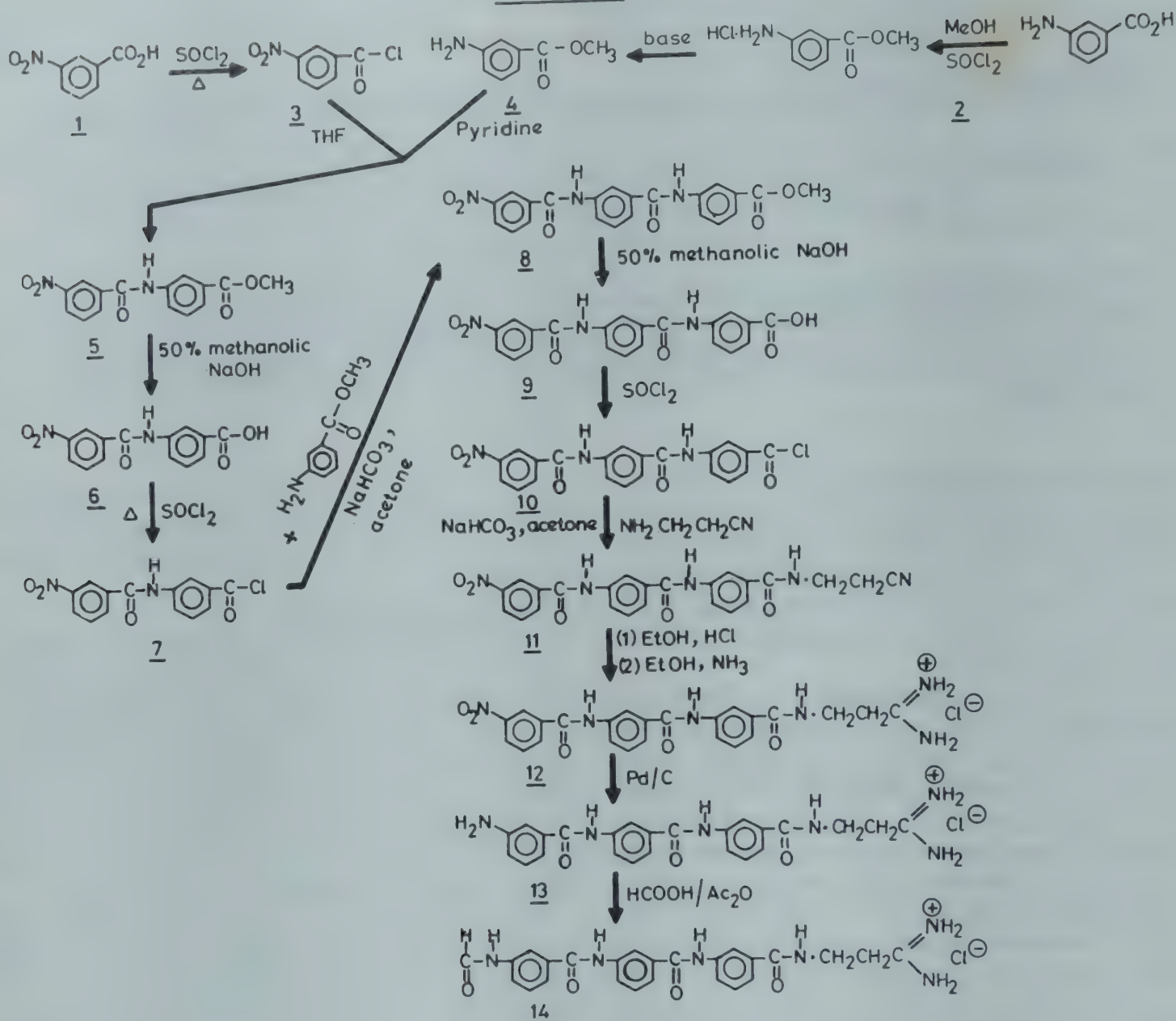
The synthetic methodology adopted for the trimer is shown in Scheme 1. The starting materials for the formation of the trimer were 3-aminobenzoic acid (2) and 3-nitrobenzoic acid (1). Coupling between 3-nitrobenzoic acid chloride (3) and 3-aminomethyl benzoate (4) gave rise to the dimer ester (5) and hydrolysis of 5 led to the dimer acid (6). This acid was converted into the acid chloride (7) and then the steps to obtain the trimer (14) followed.

The UV spectrum of the TLC purified trimer (14) was featureless with no distinct peak. The PMR spectrum of the same sample showed a number of signals some of which did not correspond to any of the functional groups in the molecule. Hence, HPLC purification was necessitated.

Purification by HPLC entailed using of methanol as the eluent. The trimer (2 mg) was dissolved in methanol (1 ml). An aliquot of the sample solution was loaded on the reverse phase column which was equilibrated with 100 % methanol at a flow rate of 1 ml/min. The UV absorbance of the eluted peaks was monitored at 300 nm. Two sharp peaks were obtained at retention times of 2 min and 2.72 min and a third, broad peak appeared at a retention time of 25.5 min. All the three peaks were collected and their UV spectra recorded. The major peak showed a well-defined UV spectrum with a distinct  $\lambda_{\text{max}}$  at 291.7 nm-292.0 nm.

A 270 MHz PMR spectrum of this sample in D<sub>2</sub>O was recorded and it was observed that the earlier non-identifiable peaks were non-existent. In fact, all the peaks corresponded to specific functional groups in the molecule. The yield was 1.06 mg (75 %).

SCHEME 1



### Experimental Procedure

Melting points were determined on a Reichert melting point apparatus and are uncorrected. The IR spectra of the intermediates were checked on 297 and 599 Perkin-Elmer spectrophotometers and only the principle bands are reported ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ). The PMR spectra of the compounds were recorded on a Varian T-60 (60 MHz) or a T-90 (90 MHz) spectrophotometer or a Bruker WH270 FT (270 MHz) instrument as the case may be.

The mass spectra were recorded on a VG Micro-mass 7070H with electron energy of 70 eV. The emission current was 200A with a source temperature of  $180^\circ\text{C}$ . Elemental analyses were conducted on a C,H,N,S,O automatic Carlo-Erba analyses. Homogeneity of the compounds were checked by TLC on silica gel G plates. A Beckman HPLC system equipped with a superrac fraction collector was utilized and purification was carried out on a Lichro-

sorb RP-18 column of diameter  $4 \times 250$  mm (particle size 5 and 10 micron). An injection loop of  $20 \mu\text{l}$  capacity was used. Uvasol methanol was the eluent.

### Methyl 3-[3-nitrobenzamido]benzoate (5)

3-Nitrobenzoic acid (1, 2.1 g, 12 mmol) was refluxed with thionyl chloride (7 ml) for 3 hr. The thionyl chloride was evaporated with benzene as the co-solvent to ensure complete removal of thionyl chloride. A yellow-white low melting solid (3) was obtained.

To absolute methanol (8 ml), cooled in an ice-salt bath, distilled thionyl chloride (0.8 ml) was added dropwise. To this solution, 3-aminobenzoic acid (2, 1 g, 8 mmol) was added and the reaction was continued for 10 hr at room temperature with stirring. Methanol was evaporated *in vacuo* along with traces of thionyl chloride. This was filtered and washed with ether and stored. To obtain methyl 3-aminob-

enzoate (**4**), the ester hydrochloride was neutralised with saturated sodium bicarbonate solution and then extracted with chloroform. Chloroform extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to furnish **4** as a brown oil, yield 0.644 g (80 %); m.p. 38 (lit.<sup>12</sup> m.p. 39). Compounds **3** and **4** were prepared prior to coupling as they are unstable compounds.

Compound **3** (2.24 g, 12 mmol) was dissolved in dry tetrahydrofuran (THF) (9ml) and the solution was added dropwise to a solution of **4** (1.8 g, 12 mM) in dry THF (9ml) containing pyridine (1 ml). The white mixture was stirred in an ice-bath ensuring the reaction mixture was free of moisture for 2 hr. THF and pyridine were removed and the solid was thoroughly washed with dilute acid, dilute alkali and water to get pure **5** as a brown solid, yield 2.54 g (74 %); m.p. 211-15°; IR (Nujol) : 3300, (N-H), 1730, (C=O, ester), 1650, (C=O, amide) 1580; (C-NO<sub>2</sub>); PMR (DMSO-*d*<sub>6</sub>, 60 MHz) : 10.79 (*s*, 1H, N-H), 8.87-7.53 (*m*, 8H, Ar-H), 3.89 (*s*, 3H, -OCH<sub>3</sub>) (Found : C, 60.8; H, 4.3; N, 9.1. C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub> requires C, 60.0; H, 4.0; N, 9.3%).

### 3-(3-Nitrobenzamido) benzoic acid (**6**)

Compound **5** (3 g, 10 mmol) was dissolved in methanol (20 ml) and stirred. To this solution, a solution of 50 % methanolic 2N NaOH (24 ml) was added and stirring continued for 2 hr. The solution was filtered, the mixture evaporated free of methanol and to the remaining solution, 1N HCl was added until the pH of the solution was 2 when a thick white precipitate formed. This was filtered and washed thoroughly with water and dried to give **6**, yield 2.75 g (96 %); m.p. 202-5°; IR (Nujol) : 3300, (N-H), 1700, (C=O, acid), 1650, (C=O, amide), 1580, (C-NO<sub>2</sub>); PMR (DMSO-*d*<sub>6</sub>, 60 MHz) : 10.50 (*bs*, 1H, N-H), 8.9-7.2 (*m*, 8H, Ar-H) (Found : C, 59.2; H, 3.6; N, 10.1. C<sub>14</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub> requires C, 58.7; H, 3.5; N, 9.8 %).

### 3-(3-Nitrobenzamido) benzoyl chloride (**7**)

A mixture of **6** (1.5g, 5mmol) and thionyl chloride (5ml) was refluxed for 4 hr. Thionyl chloride was evaporated with benzene as co-solvent to give **7** as a solid. Compound **7** was not isolated as it was unstable and was immediately used in the coupling reaction with **4**.

### Methyl 3-[3-(3-nitrobenzamido)benzamido]-benzoate (**8**)

A solution of **7** (1g, 3.3 mmol) in acetone (10ml) was added dropwise to a solution of hydrochloride salt of **4** (695 mg, 3.7 mmol) in 4 % NaHCO<sub>3</sub> (21 ml) and acetone (11ml) in an ice-bath. Stirring was continued for 10-12 hr when **8** separated as a solid.

Acetone was evaporated, the residue was filtered and washed with dilute alkali, dilute acid and water alternately and finally with water. Compound **8** thus obtained was dried *in vacuo*, yield 1.03 g (75 %); m.p. 196-98°; IR (Nujol) : 3300 (N-H), 1740 (C=O, ester), 1650 (C=O, amide), 1580 (C-NO<sub>2</sub>); PMR (DMSO-*d*<sub>6</sub>, 60 MHz) : 10.70 (*bs*, 1H, N-H), 10.36 (*bs*, 1H, N-H), 9.0-8.93 (*m*, 2H, Ar-H), 8.53-7.2 (*m*, 10H, Ar-H), 3.90 (*s*, 3H, -OCH<sub>3</sub>) (Found : C, 62.7; H, 4.4; N, 10.8. C<sub>22</sub>H<sub>17</sub>N<sub>3</sub>O<sub>6</sub> requires C, 63.0; H, 4.1; N, 10.0 %).

### 3-[3-(3-nitrobenzamido)benzamido] benzoic acid (**9**)

Compound **8** (1g, 2.4 mmol) was suspended in methanol (6 ml) and stirred. To this solution, a solution of 50 % methanolic 2N NaOH (8ml) was added and stirring continued for 2 hr. The solution was filtered, the filtrate was evaporated free of methanol and to the remaining solution, 1N HCl was added until the pH of the solution was 2, when a thick white precipitate formed. The precipitate was filtered, washed free of acid and dried to give **9**, yield 900 mg (92 %); m.p. 219-22°; IR (Nujol) : 3500 (O-H), 1690 (C=O, acid), 1650 (C=O, amide) 1580 (C-NO<sub>2</sub>); PMR (DMSO-*d*<sub>6</sub>, 60 MHz) : 10.9 (*s*, 1H, N-H), 10.56 (*s*, 1H, N-H), 8.93 (*t*, 2H, Ar-H), 8.83-7.33 (*m*, 8H, Ar-H) (Found : C, 62.4; H, 3.9; N, 10.5. C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>6</sub> requires C, 62.2; H, 3.7, N, 10.4 %).

### 3-[3-(3-Nitrobenzamido)benzamido]benzoyl chloride (**10**)

To **9** (705 mg, 1.7 mmol), thionyl chloride (7 ml) was added and refluxed for 4 hr. Thionyl chloride was evaporated completely using benzene as co-solvent to afford **10** as an oil which was unstable and hence, used in the next reaction immediately.

### 3-[3-(3-Nitrobenzamido)benzamido]benzamido-propionitrile (**11**)

A solution of **10** in acetone (7 ml) was added dropwise to a solution of β-aminopropionitrile fumarate (384 mg, 1.5 mmol (dissolved in a mixture of 14 ml of 4 % NaHCO<sub>3</sub> and 7 ml acetone). The *in situ* reaction maintained in an ice-bath ensured formation of β-aminopropionitrile from its fumarate salt and consequent coupling with **10**. The reaction mixture was stirred at room temperature for 10-12 hr and acetone evaporated to afford crude **11** as a solid which was filtered off, washed with dil acid, dil alkali and water and then thoroughly dried, yield 564 mg (72 %); m.p. 206-9°; IR (Nujol) : 3320 (N-H), 2240 (C≡N), 1650 (C=O, amide), 1580 (C-NO<sub>2</sub>); PMR (DMSO-*d*<sub>6</sub>, FT-90 MHz) : 10.68 (*s*, 1H, N-H), 10.35 (*s*, 1H, N-H), 8.86 (*t*, 3H, Ar-H), 8.5-

7.45 (*m*, 9H, Ar-H), 3.6 (*t*, 2H,  $-\text{CH}_2$ ), 2.7 (*t*, 2H,  $-\text{CH}_2$ ); MS :  $m/z$  457 ( $\text{M}^+$ ) (Found : C, 63.5; H, 4.7; N, 16.0.  $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O}_5$  requires C, 63.0; H, 4.2; N, 15.31 %).

3-[3-(3-Nitrobenzamido)benzamido]benzamido-propionamidinium hydrochloride (**12**)

Through a suspension of **11** (200 mg, 0.44 mmol) in absolute ethanol (11 ml), kept immersed in an ice-bath was passed dry HCl for 1-1.5 hr. On dissolution of the solid, a yellow coloured solution resulted. The solvent was evaporated and the residue washed thoroughly with distilled dry ether to remove traces of HCl vapours. A brown oil was obtained.

The oil was suspended in absolute ethanol (11 ml) and dry ammonia gas bubbled through this solution for 1 hr. The oil dissolved completely and the solution turned yellow. Ethanol was evaporated and the residue was washed with ether and dried to afford **12** as a glassy, hygroscopic yellow-brown solid. The product was identified by TLC using 20 %  $\text{CH}_3\text{OH}$  in  $\text{CHCl}_3$  and a few drops of AcOH as the system. This hygroscopic salt showed a broad IR spectrum with no  $\text{C}\equiv\text{N}$  band as observed in the IR spectrum of **11**.

3-[3-(3-Aminobenzamido)benzamido]benzamido-propionamidinium hydrochloride (**13**)

Compound **12** (150 mg, 0.31 mmol) was dissolved in distilled methanol (5 ml) and hydrogenated over 10 % Pd/C (50 mg). The catalyst was removed by filtration under  $\text{N}_2$  atmosphere and the methanol evaporated *in vacuo*. The residue was washed with ether and dried to give **13** as a white solid. This was the reduced form of **12** and was identified by TLC using 20 %  $\text{CH}_3\text{OH}$  in  $\text{CHCl}_3$  and a few drops of AcOH as the system.

Isolation of **13** was not possible as it was very hygroscopic and unstable.

3-[3-[3-(Formylamino)benzamido]benzamido]benzamido-propionamidinium hydrochloride (**14**)

To **13**, 98 % formic acid (2ml) was added and kept at room temperature for a few hours under moisture-free conditions. The formation of the product was monitored by TLC. Then freshly distilled, dry  $\text{Ac}_2\text{O}$  (0.25-0.35 ml) was added and the reaction mixture kept in the cold. The formation of the final, major product was again monitored by TLC

using 20 %  $\text{CH}_3\text{OH}$  in  $\text{CHCl}_3$  and a few drops of AcOH;  $R_f$  (retention factor) 0.1. A minor product with  $R_f = 0.8$  was also observed. On evaporation of  $\text{Ac}_2\text{O}$  and formic acid, impure product **14** was obtained.

The solid was dissolved in  $\text{CH}_3\text{OH}$  and precipitated using EtOAc. The process of precipitation was repeated several times and the remaining solution kept in cold to achieve complete precipitation. The solution was then microfuged and **14** was collected in a pre-weighed eppendorf tube. It was hygroscopic and stored in a dessicator at  $-20^\circ\text{C}$ , yield 35 mg (39 %).

Elemental analyses were not possible due to the instability of the compound. However, its PMR spectrum displayed unidentifiable peaks and HPLC purification of the impure trimer (**14**) was carried out as already described and its PMR spectrum recorded; PMR ( $\text{D}_2\text{O}$ , FT 270 MHz) : 8.25 (*s*, 1H,  $-\text{CHO}$ ), 8.0-7.48 (*m*, 12H, Ar-H), 3.72-3.46 (*t*, 2H,  $-\text{CH}_2$ ), 2.72-2.64 (*t*, 2H,  $\text{CH}_2$ ). All the N-H protons were exchangeable with  $\text{D}_2\text{O}$ .

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## A Novel Synthesis of Naphthalenic Lignan Lactones

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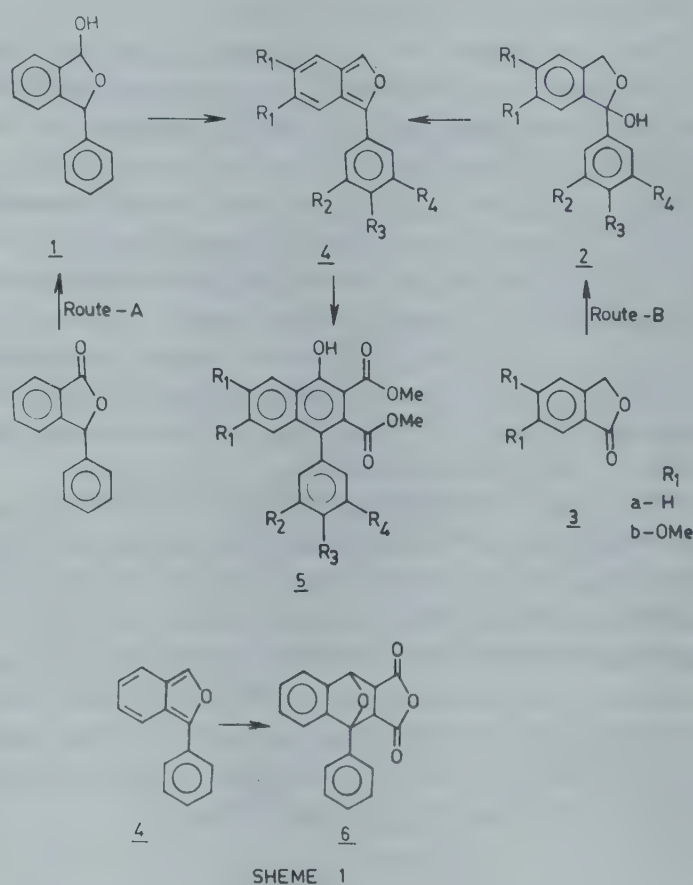
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Hydroxyphthalans (**2**) are obtained either through selective reaction of aryllithiums with phthalides (**3a,b**) or selective reduction of the formyl group in *o*-formylbenzophenones (**7**). They are then converted into naphthalenic diesters (**5**), through isobenzofuran (**4**) intermediates (generated *in situ* from hydroxyphthalans), by reaction with dimethyl acetylenedicarboxylate. The diesters are then converted into naphthalenic lignan lactones (**11**).

Isobenzofurans have been used in Diels-Alder reaction to obtain naphthalenic compounds<sup>1</sup>. The isobenzofurans themselves are obtained, generally *in situ*, from phthalides<sup>2</sup> or alkoxyphthalans<sup>3</sup>. These can also be obtained from the acetals of *o*-bromobenzaldehydes through metal halogen exchange reaction followed by reaction with aldehyde<sup>4</sup>.

Based on the report that phthalide can be reduced to hydroxyphthalan, which then would furnish the isobenzofuran by an elimination reaction<sup>5</sup>, we sought to prepare 1-hydroxy-3-phenylphthalan (**1**) by the reduction of 3-phenylphthalide, with a view to its further conversion into the naphthalenic diester (**5**) (Scheme 1, route A) and then to the lignan lactones. However, the reduction with such reducing agents as sodium borohydride, diborane, Li-liq NH<sub>3</sub> and Li-AlH<sub>4</sub>, were inconsistent and complicated and did not furnish useful results. We then considered the preparation of 3-hydroxy-3-phenylphthalan (**2**), which could also furnish the required isobenzofuran (Scheme 1, route B). Phthalan (**2**) was planned to be obtained from the phthalide (**3**) by reaction with an organometallic compound. Phthalides have been reacted with Grignard reagents<sup>6</sup>, where, however, only diols corresponding to reaction with two mol of the reagent are obtained. It was hoped that if aryllithium reagents were used, the reaction conditions, to limit the reaction with only one mol of the organometallic reagent, could be realised.

In the first reaction the phthalide (**3a**) was treated with one mol of phenyllithium at room temperature. The major product was *o*-(diphenyl-hydroxymethyl) benzyl alcohol†, corresponding to reaction with two mol of phenyllithium. Considerable amount of starting phthalide was recovered in the reaction. The reaction was then carried out at -78°. The crude reaction mixture did not show the presence of any *o*-(diphenyl-



hydroxymethyl) benzyl alcohol (TLC). On work-up it gave a compound which was identified by PMR as 3-hydroxy-3-phenylisobenzofuran (**2a**, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H). Compound **2a** was sensitive to heat, acid and base. It was, therefore, not rigorously purified, but was condensed with dimethyl acetylenedicarboxylate (DMAD) in the presence of *p*-toluenesulphonic acid (*p*TSA). The acid catalysis was to generate the isobenzofuran (**4**) which would then react with DMAD present to afford **5a**. The reaction indeed gave **5a**.

Similar strategy was then used and three other 1-arylnaphthalenic diesters (**5**) were obtained. The phthalides, the aryllithium reagents and the dienophiles used in the reaction and the adducts obtained

† All the compounds have been characterized by analytical and spectral data, which are given under experimental.

Table 1—Conditions Employed for obtaining Adducts (5) from Phthalide (3)

Phthalide	Reagent* /°C	Dienophile /catalyst	Adduct	Yield %	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
3a	(i) -78	DMAD/ <i>p</i> TSA	5a	60	H	H	H	H
3a	(ii) RT	DMAD/ <i>p</i> TSA	5b	50	H	OM <sub>e</sub>	OMe	H
3b	(i) -78	DMAD/ <i>p</i> TSA	5c	55	OMe	H	H	H
3b	(ii) RT	DMAD/ <i>p</i> TSA	5d	25	OMe	OMe	OMe	H
3a	(i) -78	MA†/AcOH	6	60	—	—	—	—

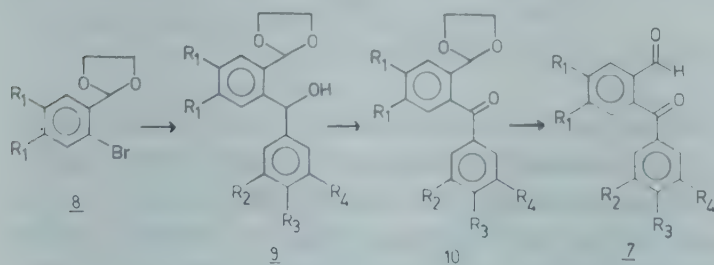
\* (i) Phenyllithium; (ii) 3,4-dimethoxyphenyllithium

† MA = maleic anhydride

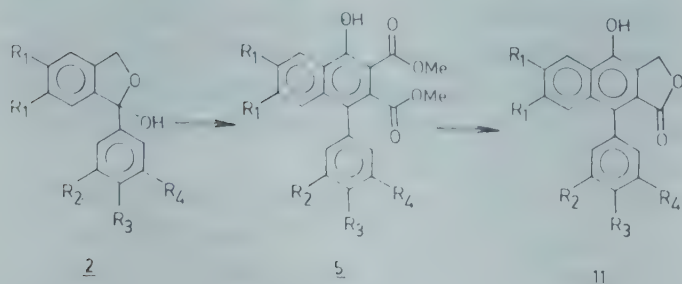
are shown in Table 1. In one case, where maleic anhydride was used, the adduct (6) with bridge oxygen was obtained as a mixture of *exo* and *endo* stereoisomers. This indicated the formation of isobenzofuran (4).

We then sought for another route to obtain the 1-hydroxy-1-arylphthalans (2). It was envisaged that if *o*-formylbenzophenones (7) could be selectively reduced at the formyl group, they can provide the required phthalan (2). The *o*-formylbenzophenones (7d to 7g) were obtained by (i) preparation of the *ortho*-lithio derivatives of the acetals of aromatic aldehydes from the corresponding bromo compounds (8)<sup>7</sup>, (ii) reaction of the lithio derivatives with aromatic aldehydes to give 9, (iii) oxidation of alcohols (9) to ketones (10) and (v) hydrolysis of the keto-acetals (10) to *o*-formylbenzophenones (7) (Scheme 2).

Thus, the *o*-formylbenzophenone (7e) on reduction with sodium borohydride and purification by crystallisation gave 3-hydroxy-3-arylphthalan (2e). On reaction with DMAD in the presence of *p*TSA, it gave 5e (Scheme 3). In other cases, the hydroxyphthalans, being unstable, were not purified but were converted into the naphthalenic diesters by reaction with DMAD/*p*TSA. The compounds prepared by the above method are listed in Table 2.



SCHEME 2



SCHEME 3

Table 2—Formation of Adducts (5) from *o*-Formylbenzophenones (7)

Compound	Adduct	R <sub>1</sub>	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
7d	5d	OMe	OMe	OMe	OMe	H
7e	5e	OMe	OMe	H	OMe	H
7f	5f	O—CH <sub>2</sub> —O	O—CH <sub>2</sub> —O	O—CH <sub>2</sub> —O	O—CH <sub>2</sub> —O	H
7g	5g	O—CH <sub>2</sub> —O	O—CH <sub>2</sub> —O	OMe	OMe	OMe

In contrast to the earlier method, where 5d was obtained in 25% yield (from 3b), the present method furnished 5d in 60% yield (from 7d).

The naphthalenic diesters 5a, 5d, 5e were then reduced with sodium borohydride in methanol<sup>7</sup> to furnish the corresponding naphthalenic lignan lactones 11a, 11d and 11e. The other naphthalenic diesters 5f, 5g have already been converted<sup>4</sup> into naturally occurring taiwanin E<sup>8</sup> and tetrahydrodopodophyllo-toxin<sup>9</sup>.

### Experimental Procedure

#### Reaction of phthalide with phenyllithium at room temperature

To a well stirred solution of phthalide (3a, 2.5 mmol) in dry ether (25 ml) at room temperature, phenyllithium (2.5 mmol in ether) was added dropwise during 10 min. The reaction mixture was stirred for 15 min and decomposed by addition of water (10 ml). The ether layer was dried and solvent removed *in vacuo*. The residue was crystallised from hexane to give *ortho*-(diphenyl hydroxymethyl) benzyl alcohol m.p. 163°, yield 45% (Found: C, 82.9; H, 6.2. C<sub>20</sub>H<sub>18</sub>O<sub>2</sub> requires C, 82.8; H, 6.2%); IR (nujol): 3350-3450, 3200-3300 (OH) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 7.3 (14H, s, 14 × Ar-H), 4.7 (1H, bs, —OH), 4.4 (2H, d, *J* = 4 Hz, —CH<sub>2</sub>—OH), 2.5 (1H, bs, —OH).

**Reaction of phthalide with phenyllithium at -78°.** The above experiment was carried out at -78° to give 2a (R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H) as a thick oil in 70% yield; analytical sample of the compound could not be obtained because of its instability.

*Diels-Alder reaction of phthalan (2a) with maleic anhydride*

The crude **2a** (1 mmol) was dissolved in toluene (40 ml) and heated to reflux with maleic anhydride (4 mmol) for 10 min, in the presence of a trace of acetic acid. Toluene was evaporated under reduced pressure, residue washed with water, filtered, dried and triturated with ether to give **6** as a mixture of *exo* and *endo* isomers, m.p. 178–82° (hexane); 60% yield (Found: C, 74.0, H, 4.2. C<sub>18</sub>H<sub>12</sub>O<sub>4</sub> requires C, 73.8; H, 4.0%); IR (nujol): 1850, 1800 cm<sup>-1</sup> (anhydride CO); PMR (CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>): δ 6.8–7.8 (9H, *m*, 9 × Ar-H), 6.2 (1H, *d*, *J* = 3 Hz, bridgehead H of *endo*-isomer), 6.0 (1H, *s*, bridgehead H of *exo*-isomer), 4.2 (2H, *m*, COCHCHCO).

*Dimethyl 4-hydroxy-1-phenylnaphthalene-2, 3-dicarboxylate (5a)*

Crude **2a** (1 mmol) was dissolved in benzene (50 ml) and heated to reflux with dimethyl acetylenedicarboxylate (2 mmol) for 2 hr in the presence of a trace of *p*-toluenesulphonic acid (*p*TSA). The residue, after flash chromatography on silica gel, elution with benzene – 5% ethyl acetate, afforded **5a**; m.p. 144° (dichloromethane/hexane); 60% yield (Found: C, 71.4; H, 4.8. C<sub>20</sub>H<sub>16</sub>O<sub>5</sub> requires C, 71.4; H, 4.8%); IR (nujol): 1735, 1660 (ester CO) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 12.3 (1H, *s*, –OH), 8.42 (1H, *dd*, *J* = 6, 2 Hz, Ar-H), 7.2–7.5 (8H, *m*, 8 × Ar-H), 3.92, 3.49 (6H, 2*s*, 2 × OMe).

*Dimethyl 4-hydroxy-6, 7-dimethoxy-1-phenylnaphthalene-2, 3-dicarboxylate (5c)*

The phthalide (**3b**, 1 mmol) on reaction with phenyllithium as above in THF (20 ml), gave a thick oil, which was converted without purification into adduct **5c**, m.p. 171° (dichloromethane/hexane); 55% yield (Found: C, 66.4; H, 5.2. C<sub>22</sub>H<sub>20</sub>O<sub>7</sub> requires C, 66.7; H, 5.1%); IR (nujol): 1750, 1650 (ester CO) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 12.2 (1H, *s*, –CH), 7.7 (1H, *s*, Ar-H); 7.3 (5H, *m*, 5 × Ar-H), 6.7 (1H, *s*, Ar-H), 4.1, 4.0, 3.7, 3.5 (12H, 4*s*, 4 × OMe).

*Dimethyl 4-hydroxy-1-(3,4-dimethoxyphenyl) naphthalene-2, 3-dicarboxylate (5b)*

To a well stirred solution of 3, 4-dimethoxybromobenzene (1 mmol) in ether (25 ml) at 0°, butyllithium (1.2 mmol in ether) was added. The resulting mixture was stirred for 45 min and to this was added a solution of phthalide (**3a** 1 mmol) in ether (15 ml) at room temperature during 10 min, stirred for further 15 min and decomposed with water (10 ml). The organic layer on drying and removal of solvent gave a thick oil, which was converted into adduct **5b**; m.p. 161° (dichloromethane/hexane); 50% yield (Found: C, 67.0; H, 5.0.

C<sub>22</sub>H<sub>20</sub>O<sub>7</sub> requires C, 66.7; H, 5.1); IR (nujol): 1710, 1660 (ester CO) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 12.2 (1H, *s*, –OH), 8.4 (1H, *m*, Ar-H), 7.5 (3H, *m*, 3 × Ar-H), 6.8 (3H, *m*, 3 × Ar-H), 3.9, 3.8, 3.6 (12H, 3*s*, 4 × OMe).

*Dimethyl 4-hydroxy-6, 7-dimethoxy-1-(3, 4-dimethoxyphenyl)naphthalene-2, 3-dicarboxylate (5d)*

Using phthalide **3b** in THF (20 ml) in the previous experiment, adduct **5d** was obtained; m.p. 180° (dichloromethane/hexane); 25% yield (Found: C, 62.9; H, 5.6. C<sub>24</sub>H<sub>24</sub>O<sub>9</sub> requires C, 63.2; H, 5.3%); IR (nujol): 1730, 1660 (ester CO) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 12.3 (1H, *s*, –OH), 7.7 (1H, *s*, Ar-H), 6.9 (3H, *m*, 3 × Ar-H), 6.8 (1H, *s*, Ar-H), 4.1, 4.0, 3.8, 3.6 (18H, 5*s*, 6 × OMe).

**Hydroxyacetals (9)**

*General procedure*

To a solution of the bromoacetal (**8**) (10 mmol) in THF (40 ml), *n*-BuLi (11 mmol in ether) was added at –78°. After 15 min, a solution of aromatic aldehyde (11 mmol) in THF (15 ml) was added. After being stirred for 30 min at –78°, the reaction mixture was decomposed with water and THF removed under reduced pressure. The aqueous layer was extracted with ether. Washing of ether extract with water, drying and evaporation gave the hydroxyacetal (**9**).

Thus were obtained the following hydroxyacetals (**9**) (i) α-2-[1, 3-Dioxolan-2-yl]-4, 5-dimethoxyphenyl]-3,4-dimethoxybenzyl alcohol (**9d**: R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = OMe, R<sub>4</sub> = H); m.p. 133° (ether), analytical sample of the compound could not be obtained due to its instability; 75% yield.

(ii) α-2-[(1,3-Dioxolan-2-yl)-4, 5-dimethoxyphenyl]-4-methoxybenzyl alcohol, (**9e** R<sub>1</sub> = R<sub>3</sub> = OMe, R<sub>2</sub> = R<sub>4</sub> = H) m.p. 106–8° (ether); 80% yield (Found: C, 65.8; H, 6.4; C<sub>19</sub>H<sub>22</sub>O<sub>6</sub> requires C, 65.9; H, 6.4%); IR (nujol): 3475 (OH) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 7.25 (2H, *dJ* = 8 Hz, 2 × Ar-H), 7.06 (1H, *s*, Ar-H), 6.8 (3H, *d*, *J* = 8 Hz, 3 × Ar-H), 6.06 (1H, *s*, –CH–OH), 5.84 (1H, *s*, O–CH–O), 4.05 (4H, *m*, O–CH<sub>2</sub>–CH<sub>2</sub>–O), 3.88, 3.78, 3.75 (9H, 3*s*, 3 × OMe), 3.2 (1H, *bs*, –OH).

(iii) α-2-[(1, 3-Dioxolan-2-yl)-4, 5-methylenedioxyphenyl]-3,4-methylenedioxybenzyl alcohol, (**9f**, R<sub>1</sub> R<sub>1</sub> = R<sub>2</sub> R<sub>3</sub> = OCH<sub>2</sub>O, R<sub>4</sub> = H); oil, 80% yield; analytical sample of the compound could not be obtained due to its instability.

(iv) α-2-[(1, 3-Dioxolan-2-yl)-4, 5-methylenedioxyphenyl]-3, 4, 5-trimethoxybenzyl alcohol (**9g**, R<sub>1</sub> R<sub>1</sub> = OCH<sub>2</sub>O, R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = OMe); oil, 78% yield; analytical sample of the compound could not be obtained due to its instability.

**Ketoaldehydes (7)***General procedure*

To a solution of the hydroxyacetals (**9**, 5 mmol) in dry benzene at room temperature was added DDQ (5.5 mmol) in 5-6 portions. The black green coloured mixture was stirred for 3 to 4 hr during which the colour of the solution turned to buff. The benzene solution was washed with water, aq.  $\text{NaHCO}_3$ , dried, concentrated to its original volume (20 ml), and vigorously stirred at room temperature with 2  $\text{NH}_2\text{SO}_4$  for 3 hr. Filtration of resulting precipitate afforded the ketoaldehydes (**7**), characterisation data of which are given below.

(i) 2'-Formyl-4', 5'-dimethoxy-4, 5-dimethoxybenzophenone (**7d**), m.p.  $130^\circ$  (benzene/ethyl acetate); 62% yield (Found: C, 65.6; H, 5.3.  $\text{C}_{18}\text{H}_{18}\text{O}_6$  requires C, 65.5; H, 5.45%).

(ii) 2-Formyl-4,4',5'-trimethoxybenzophenone (**7e**), m.p.,  $146.5-47.5^\circ$  (hexane/ethyl acetate); 65% yield (Found: C, 67.9; H, 5.3.  $\text{C}_{17}\text{H}_{16}\text{O}_5$  requires C, 68.0; H, 5.4%); IR (nujol): 1710, 1600 (CHO, CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  9.83 (1H, s, Ar-CHO), 7.78 (2H, d,  $J=9\text{Hz}$ ,  $2 \times \text{Ar-H}$ ), 7.53 (1H, s, Ar-H), 6.96 (1H, s, Ar-H), 6.93 (2H, d,  $J=9\text{Hz}$ , Ar-H), 4.0, 3.93, 3.88 (9H, 3s,  $3 \times \text{OMe}$ ).

(iii) 2'-Formyl-4, 5, 4', 5'-dimethylenedioxybenzophenone (**7f**) m.p.  $133-34^\circ$  (hexane/ethyl acetate); 60% yield (Found: C, 64.3; H, 3.4.  $\text{C}_{16}\text{H}_{10}\text{O}_6$  requires C, 64.4; H, 3.4%); IR (nujol): 1690, 1650 (CHO, CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  9.78 (1H, s, Ar-CHO), 7.46 (1H, s, Ar-H), 7.37 (1H, d,  $J=2\text{Hz}$ , Ar-H), 7.3 (1H, dd,  $J=9, 2\text{Hz}$ , Ar-H), 6.9 (1H, s, Ar-H), 6.82 (1H, d,  $J=9\text{Hz}$ , Ar-H), 6.14, 6.06 (4H, 2s,  $2 \times \text{O}-\text{CH}_2-\text{O}$ ).

(iv) 2'-Formyl-4', 5'-methylenedioxy-3, 4, 5-trimethoxybenzophenone, (**7g**), m.p.  $168.5-69.5^\circ$  (hexane-ethyl acetate); 60% yield (Found: C, 62.6; H, 4.7.  $\text{C}_{18}\text{H}_{16}\text{O}_7$  requires C, 62.8; H, 4.7%).

**1,3-Dihydro-5,6-dimethoxy-****1-(4'-methoxyphenyl)isobenzofuran-1-ol (2e)**

To a solution of **7e** (2 mmol) in THF/ethanol (40/60, 20 ml) at  $0^\circ$  was added  $\text{NaBH}_4$  (0.5 mmol). The resulting mixture was stirred for 15 min at room temperature. Solvent was removed *in vacuo* and the thick oily residue washed with water to obtain **2e**; m.p.  $120-21^\circ$  (hexane/ethyl acetate); 86% yield (Found: C, 67.6; H, 6.0.  $\text{C}_{17}\text{H}_{18}\text{O}_5$  requires C, 67.5; H, 6.0%); IR (nujol): 3440 (OH)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  7.76 (2H, d,  $J=9\text{Hz}$ ,  $2 \times \text{Ar-H}$ ), 6.9-7.05 (4H, m,  $4 \times \text{Ar-H}$ ), 4.5 (2H, bs,  $-\text{CH}_2-\text{O}$ ), 3.99, 3.90, 3.8 (9H, 3s,  $3 \times \text{OMe}$ ), 1.7 (1H, bs,  $-\text{OH}$ ).

**Reduction of ketoaldehydes (7) and conversion to naphthalenic diesters (5) by Diels-Alder reaction: General procedure**

The keto aldehyde (**7**) was reduced with  $\text{NaBH}_4$  as

above. The residue obtained and dimethyl acetylenedicarboxylate (3 mmol) were dissolved in benzene and heated to reflux for 2 hr in the presence of a trace of *p*TSA. Solvent was evaporated and residue subjected to flash chromatography on silica gel using hexane-ethyl acetate as eluent to yield the naphthalenic esters (**5**) which are listed below.

(i) Dimethyl 4-hydroxy-6, 7-dimethoxy-1-(3', 4'-dimethoxyphenyl)naphthalene-2, 2-dicarboxylate (**5d**), m.p.  $180^\circ$  (dichloromethane/hexane), 60% yield; identical in all respects with an authentic sample.

(ii) Dimethyl 4-hydroxy-6, 7-dimethoxy-1-(4'-methoxyphenyl)naphthalene-2, 3-dicarboxylate (**5e**), m.p.  $189-90^\circ$  (ethyl acetate), 60% yield (Found: C, 64.8; H, 5.1.  $\text{C}_{23}\text{H}_{22}\text{O}_8$  requires C, 64.8; H, 5.2%); IR (nujol): 1755, 1665 (ester CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  12.22 (1H, s, OH), 7.7 (1H, s, Ar-H), 7.2 (2H, d,  $J=9\text{Hz}$ ,  $2 \times \text{Ar-H}$ ), 6.92 (2H, d,  $J=9\text{Hz}$ ,  $2 \times \text{Ar-H}$ ), 6.98 (1H, s, Ar-H), 4.0, 3.95, 3.9, 3.75, 3.5 (15H, 5s,  $5 \times \text{OMe}$ ).

(iii) Dimethyl 4-hydroxy-6, 7-methylenedioxy-1-(3', 4'-methylenedioxyphenyl) naphthalene-2, 3-dicarboxylate (**5f**), m.p.  $191-92^\circ$  (ethanol); 60% yield (Found: C, 62.3; H, 4.1.  $\text{C}_{22}\text{H}_{16}\text{O}_9$  requires C, 62.3; H, 3.8%); PMR ( $\text{CDCl}_3$ ):  $\delta$  12.14 (1H, s,  $-\text{OH}$ ), 7.7 (1H, s, Ar-H), 6.7-6.9 (4H, m,  $4 \times \text{Ar-H}$ ), 6.02 (4H, s,  $2 \times \text{O}-\text{CH}_2-\text{O}$ ), 3.92, 3.58 (6H, 2s,  $2 \times \text{OMe}$ ).

(iv) Dimethyl 4-hydroxy-6, 7-methylenedioxy-1-(3', 4', 5'-trimethoxyphenyl) naphthalene-2, 3-dicarboxylate (**5g**), m.p.  $241-42^\circ$  (ethanol/ethyl acetate); 60% yield (Found: C, 61.2; H, 4.7.  $\text{C}_{24}\text{H}_{22}\text{O}_{10}$  requires C, 61.3; H, 4.7%); PMR ( $\text{CDCl}_3$ ):  $\delta$  12.21 (1H, s,  $-\text{OH}$ ), 7.77 (1H, s, Ar-H), 6.81 (1H, s, Ar-H), 6.56 (2H, s,  $2 \times \text{Ar-H}$ ), 6.1 (2H, s,  $\text{O}-\text{CH}_2-\text{O}$ ), 4.0, 3.9, 3.63 (15H, 3s,  $5 \times \text{OMe}$ ).

**Reduction of (5) to naphthalenic lignan lactones (11): General procedure**

The diester (**5**, 0.25 mmol) in THF/methanol (20 ml) was treated with portions of  $\text{NaBH}_4$  ( $3 \times 0.5\text{ g}$ ) at room temperature during 8 hr. 2  $\text{NHCl}$  was added and the mixture stirred for a further 30 min. Removal of solvent gave the lignan lactones (**11**). Thus were prepared **11a**, **11d** and **11e**.

(i) 4-Hydroxy-9-phenylnaphtho[2,3-c]furan-1-(3H)-one (**11a**); m.p.  $174^\circ$  (chloroform); 65% yield (Found: C, 78.1; H, 4.3.  $\text{C}_{18}\text{H}_{12}\text{O}_3$  requires C, 78.3; H, 4.4%); IR (nujol): 3550 (OH), 1750 (ester CO)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  9.9 (1H, bs,  $-\text{OH}$ ), 8.4 (1H, m, Ar-H), 7.4 (8H, m,  $8 \times \text{Ar-H}$ ), 5.25 (2H, s,  $-\text{CH}_2-\text{O}$ ).

(ii) 4-Hydroxy-6,7-dimethoxy-9-(3, 4-dimethoxyphenyl)-naphtho[2, 3-c]-furan-1-(3H)-one (**11d**); m.p.  $185^\circ$  (dichloromethane); 67% yield (Found: C, 66.3; H, 5.1.  $\text{C}_{22}\text{H}_{20}\text{O}_7$  requires C, 66.7; H, 5.1%); IR (nujol): 3390 (OH), 1750 (ester CO)  $\text{cm}^{-1}$ ; PMR

(CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>):  $\delta$  9.7 (1H, *s*, —OH), 7.7 (1H, *s*, Ar-*H*), 7.1 (1H, *s*, Ar-*H*), 6.9 (3H, *m*, 3  $\times$  Ar-*H*), 5.3 (2H, *s*, —CH<sub>2</sub>—O), 4.1, 4.0, 3.9, 3.8 (12H, 4*s*, 4  $\times$  OMe).

(iii) 4-Hydroxy-6, 7-dimethoxy-9-(4-methoxy-phenyl)naphtho [2, 3-*c*]furan-1-(3*H*)-one (**11e**); m.p. 280-81° (acetone); 76% yield (Found: C, 68.9; H, 5.0. C<sub>21</sub>H<sub>18</sub>O<sub>6</sub> requires C, 68.8; H, 5.0%); IR (nujol): 3150 (OH); 1725 (ester CO) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>):  $\delta$  9.65 (1H, *bs*, —OH), 7.65 (1H, *s*, Ar-*H*), 7.26 (2H, *d*, *J* = 9Hz, 2  $\times$  Ar-*H*), 7.0 (3H, *m*, 3  $\times$  Ar-*H*), 5.37 (2H, *s*, —CH<sub>2</sub>—O), 4.07, 3.90, 3.76 (9H, 3*s*, 3  $\times$  OMe).

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## An Efficient Synthesis of Naphthalenic Lignan Lactones

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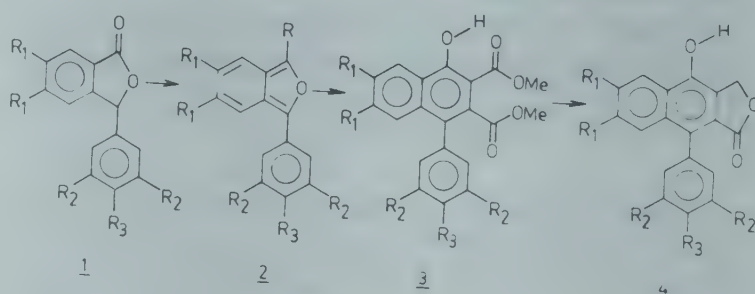
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Phthalides (**1a-c**) have been converted into the corresponding naphthalenic diesters (**3a-c**) and anhydrides (**11,15**), through silyloxyisobenzofurans (**2a-c**), generated *in situ*, by reaction with respective dienophiles. The naphthalenic lignan lactones (**4a-c**), including naturally occurring tetrahydrodopodophyllotoxin, have been obtained from the diesters and the anhydrides, by selective reduction of the carbonyl group.

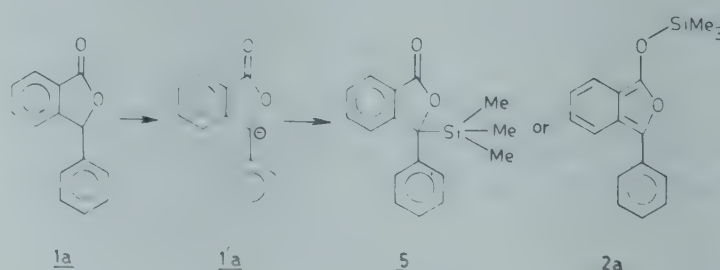
The conversion of phthalide into 1-hydroxy-2,3-carbomethoxynaphthalene by treatment with LDA, followed by dimethyl fumarate was reported by Broom and Sammes<sup>1</sup>. With a view to converting 3-arylphthalides into 1-arylnaphthalenic compounds, in particular to the naphthalenic lignan lactones (**4**), 3-phenylphthalide (**1a**;  $R_1 = R_2 = R_3 = H$ ) was treated with LDA at  $-10^\circ$ . Further reaction with ethyl acrylate, dimethyl fumarate and maleic anhydride, under a variety of experimental conditions, however, failed to yield any product. In an alternate approach, the possibility of converting the phthalides to isobenzofurans (**2**), specifically the silyl ether (**2**;  $R = OSiMe_3$ ), and condensing with different dienophiles in a Diels-Alder reaction, was considered (Scheme 1). The isobenzofurans<sup>2</sup> (**2**,  $R = H$ ) indeed have been used in Diels-Alder reaction to provide the naphthalenic compounds<sup>†</sup>. 3-Phenylphthalide (**1a**) was treated with LDA at  $-10^\circ$  (Scheme 2).

A red coloured solution was obtained, which was presumably due to the anion (**1'a**). On treatment with  $ClSiMe_3$ , the colour changed to golden yellow, indicating the consumption of the anion. In analogy with the colour reported for isobenzofuran<sup>4</sup> the product was considered to be silyloxyisobenzofuran (**2a**) and not the C-silyl compound (**5**) which is expected to be colourless. However, the compound could not be isolated and characterised.

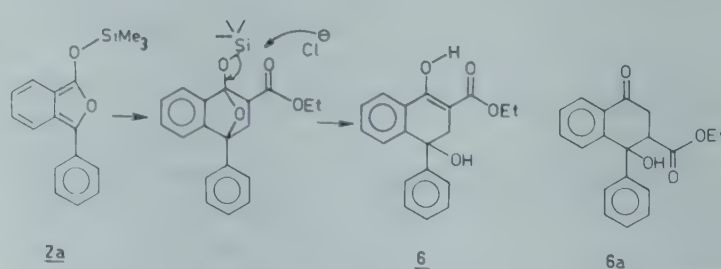
On treating compound (**5** or **2a**) with ethyl acrylate, the golden yellow colour disappeared to give a white precipitate. Further work-up gave a compound which was characterised as **6** on the basis of elemental analyses and spectral data (see Experimental). Only one regioisomer, **6**, was formed and not the other, **6a**. This was expected in a Michael reaction of **1a**, regenerated



SCHEME 1



SCHEME 2

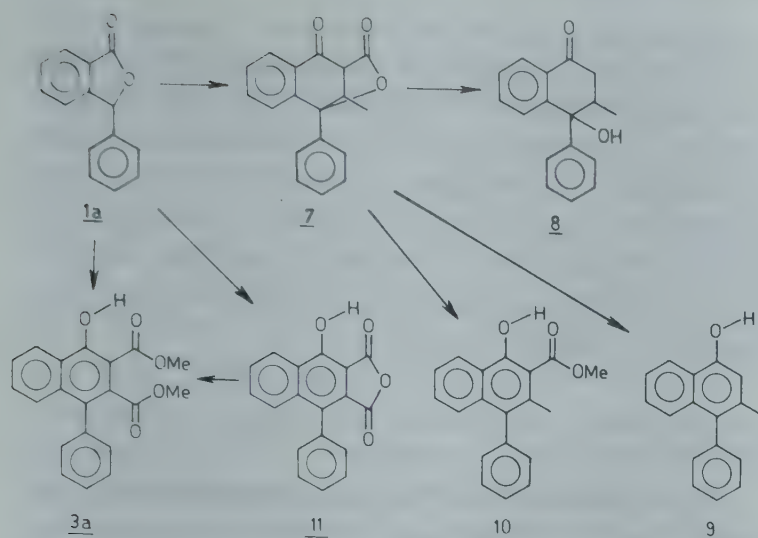


SCHEME 3

by desilylation of **2a** or **5** in the presence of nucleophiles, or in the Diels-Alder reaction of **2a** with ethyl acrylate, where formation of the *ortho*-adduct (*ortho* to  $OSiMe_3$  and  $COOEt$ ) is the preferred reaction<sup>5</sup>. In view of the fact that the **6** was not formed from anion **1a** in the absence of  $ClSiMe_3$ , the Diels-Alder reaction was considered to be the more probable route. The mechanism of formation of **6** is shown in Scheme 3.

A similar reaction with methyl crotonate led to **7** (for spectral characterisation see Experimental). On basic hydrolysis, **7** afforded **8** by hydrolysis of the lac-

<sup>†</sup> The work described here was presented at the 'National Symposium on Natural Products' held at NCL, Pune, in 1983. It also constitutes as a part of the Ph. D thesis of Mr S M Gokhale, submitted to the University of Poona (1984). A paper on similar lines has since appeared<sup>3</sup>.



SCHEME 4

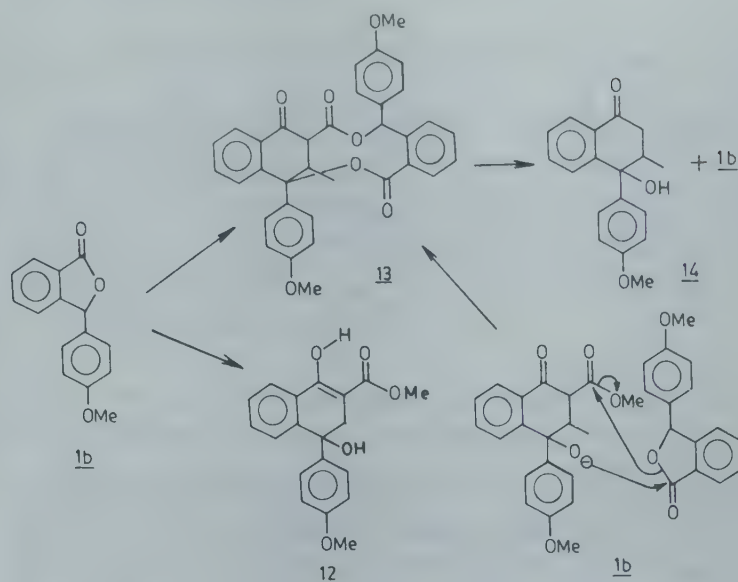
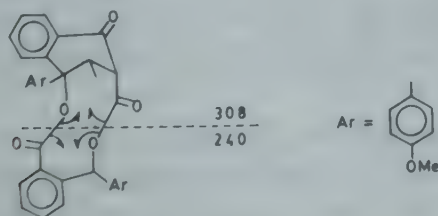
tone formed followed by decarboxylation of the resulting  $\beta$ -keto acid. On acidic hydrolysis, **7** afforded **9** evidently by dehydration of formed **8**. In order to retain the carboxylic carbon, methanolysis with MeOH/HCl was carried out, when **10** was obtained (Scheme 4).

Similar reaction of **1a** with maleic anhydride led to **11** while reaction with dimethyl fumarate led to **3a**. The anhydride (**11**) on methanolysis (MeOH/HCl) gave the diester (**3a**) (Scheme 4).

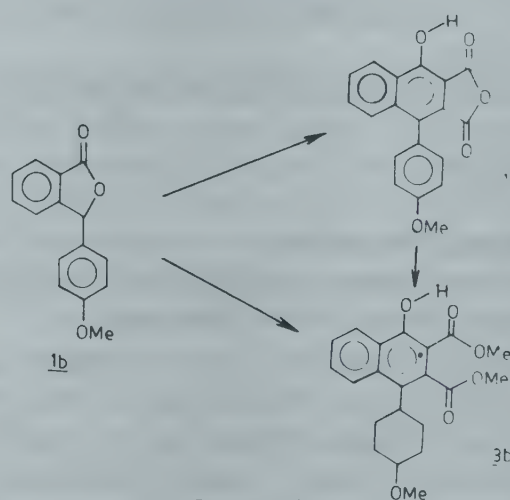
In order to determine the influence of a *para*-methoxyphenyl group on the course of the reaction, similar reactions were carried out with the phthalide (**1b**:  $R_1 = R_2 = H$ ,  $R_3 = OMe$ ). With methyl acrylate compound (**12**) was obtained. However with methyl crotonate the compound obtained was **13**. The structure was assigned on elemental analyses, mass spectrum† and PMR data (see Experimental). In agreement with the assigned structure, the compound was converted into **14** and **1b** by alkaline hydrolysis. The formation of **13** can be visualised as the reaction of the alkoxide ion (formed according to Scheme 3) with another molecule of **1b** (Scheme 5).

The reaction of **1b** with maleic anhydride led to the anhydride (**15**), and with dimethyl fumarate, the diester **3b** was obtained. The latter was also obtained by methanolysis of **15** (Scheme 6).

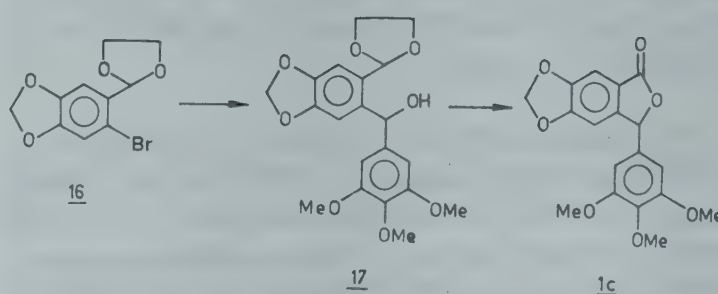
† Mass spectrum does not show  $M^+$ . However, there are two peaks at  $m/z$  308 and 240 which could be due to simultaneous cleavage of the two lactone groups, as shown below, in close proximity. The compound has the correct analysis and also three carbonyl absorption bands at 1770, 1750 and  $1690\text{ cm}^{-1}$  in its IR spectrum



SCHEME 5



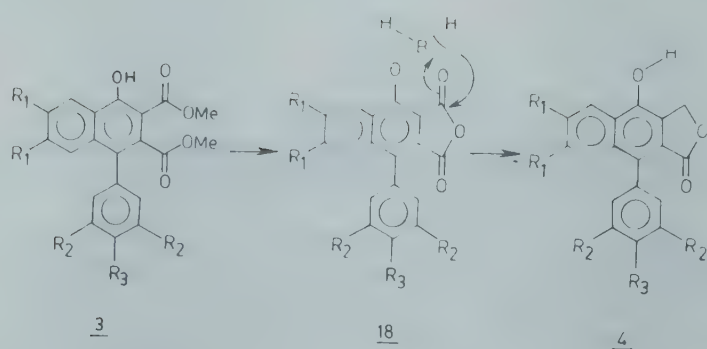
SCHEME 6



SCHEME 7

The above method was then extended to the synthesis of the naturally occurring tetrahydropodophyllotoxin<sup>6</sup> (**4c**,  $R_1R_1 = O-CH_2-O$ ,  $R_2 = R_3 = OCH_3$ ). Metal-halogen exchange reaction of the ethylene ketal of bromopiperonal (**16**) followed by reaction with trimethoxybenzaldehyde gave **17**. This on hydrolysis and oxidation furnished the required phthalide (**1c**) (Scheme 7). The reaction of **1c** with LDA, TMS and dimethyl fumarate in sequence gave **3c** ( $R_1R_1 = O-CH_2-O$ ,  $R_2 = R_3 = OCH_3$ ).

Sodium borohydride reduction of **3a**, **3b** (in DMF) and of **3c** (in methanol)<sup>7</sup> afforded the naphthalenic



SCHEME 8

lignan lactones (**4a-c**) respectively. In this reduction, the ester carbonyl group, adjacent to OH, was reduced. This was presumably because of the initial formation of boride (**18**), by reaction of sodium borohydride with the OH group, which then transferred the hydride to the carbonyl group intramolecularly (Scheme 8).

Reduction of the anhydrides **11** and **15**, using sodium borohydride in DMF gave lactones **4a** and **4b** respectively.

### Experimental Procedure

#### Treatment of 3-phenylphthalide (**1a**) with LDA and $\text{ClSiMe}_3$ and reaction with dienophiles

To an ice cold solution of LDA in THF (3 mmol) was added a solution of **1a** (2 mmol) in THF (10 ml). After complete addition (5 min) the reaction mixture was stirred for 10 min. Trimethyl chlorosilane (6 mmol) was added to the above blood red coloured solution with the help of a syringe. The colour of the solution changed to bright yellow. Stirring was continued for further 10 min.

#### (i) Reaction with ethyl acrylate: Formation of **6**

Ethyl acrylate (4 mmol) in THF (5 ml) was added dropwise to the above reaction mixture. The bright yellow colour faded and a white turbidity appeared. Stirring was continued for 30 min in the cold and for 1 hr at room temperature. Water (15 ml) was added to the reaction mixture and THF removed under reduced pressure. The reaction mixture was extracted with ether, the ether layer dried and evaporated to give a residue which, after column chromatography on silica gel using hexane-ethyl acetate (5%), gave **6**, m.p.  $119^\circ$  (benzene-hexane), 63% yield (Found: C, 75.3; H, 6.1.  $\text{C}_{19}\text{H}_{18}\text{O}_4$  requires C, 75.5; H, 6.0%); IR (nujol): 3500 (OH), 1600 (H-bonded and  $\alpha$ ,  $\beta$ -unsaturated  $\text{COOEt}$ )  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  12.35 (1H, s, —OH), 7.88 (1H, dd,  $J=6, 2$  Hz, Ar—H), 7.1–7.5 (9H, m, 9  $\times$  Ar—H), 4.16 (2H, q,  $J=7$  Hz, —O— $\text{CH}_2$ — $\text{CH}_3$ ), 3.15, 3.25 (2H, 2d,  $J=14$  Hz each,  $\text{C}=\text{C}$ — $\text{CH}_2$ ), 2.2–2.5 (1H, bs, OH), 1.22 (3H, t,  $J=7$  Hz,  $\text{OCH}_2\text{CH}_3$ )

#### (ii) Reaction with methyl crotonate: Formation of **7**

Compound **7**, m.p.  $104^\circ$  (ethanol) was obtained in 60% yield (Found: C, 77.6; H, 5.1.  $\text{C}_{18}\text{H}_{14}\text{O}_3$  requires C, 77.7; H, 5.1%); IR (nujol): 1770 (lactone CO), 1680 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  8.6 (1H, dd,  $J=6, 2$  Hz, Ar—H), 7.4–7.6 (7H, m, 7  $\times$  Ar—H), 7.05 (1H, dd,  $J=6, 2$  Hz, Ar—H), 3.78 (1H, d,  $J=5$  Hz, —CO—CH), 3.27 (1H, dq,  $J=5, 8$  Hz, CH—CH— $\text{CH}_3$ ), 1.25 (3H, d,  $J=8$  Hz, CH— $\text{CH}_3$ ).

#### (iii) Reaction with maleic anhydride: Formation of **11**

The reaction mixture was decomposed with a mixture of conc. HCl and water (1:1, 15 ml) to give a residue which after column chromatography over silica gel using dichloromethane as eluent gave **11**, m.p.  $263^\circ$  (blackens around  $260^\circ$ ) (dichloromethane), 67% yield (Found: C, 74.4; H, 3.6.  $\text{C}_{18}\text{H}_{10}\text{O}_4$  requires C, 74.5; H, 3.5%); IR (nujol): 1840 ( $-\text{C}=\text{O}$ ), 1770 ( $-\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3 + \text{DMSO}-d_6$ ):  $\delta$  8.4–8.7 (1H, dd,  $J=7.2$  Hz, Ar—H), 7.2–7.3 (5H, m, 5  $\times$  Ar—H), 7.6–7.72 (3H, m, 3  $\times$  Ar—H), 4.2–5.0 (1H, b, —OH).

#### (iv) Reaction with dimethyl fumarate: Formation of 2,3-dicarbomethoxy-4-hydroxy-1-phenylanthralene (**3a**)

Compound (**3a**), m.p.  $145^\circ$  (hexane-ethyl acetate), in 60% yield, was obtained (Found: C, 71.2; H, 4.8.  $\text{C}_{20}\text{H}_{16}\text{O}_5$  requires C, 71.4; H, 4.8%); IR (nujol): 1735 ( $\text{COOMe}$ ), 1660 ( $\text{COOMe}$ )  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  12.3 (1H, s, —OH), 8.42 (1H, dd,  $J=7, 2$  Hz, Ar—H), 7.2–7.5 (8H, m, Ar—H), 3.92, 3.49 (6H, 2s, 2  $\times$  OMe).

#### Basic hydrolysis of **7**: Formation of **8**

To a solution of **7** (2 mmol) in ethanol (10 ml) was added ethanolic potassium hydroxide (10%, 10 ml) and the resulting homogeneous solution stirred at room temperature for 12 hr. Ethanol was removed *in vacuo* and water (15 ml) added to the residue and extracted with ether. The ether extract was rejected and the basic solution was cooled and acidified with dil. hydrochloric acid. The acidic layer was extracted with ether, the ether extract dried and concentrated to give **8**, m.p.  $84^\circ$  (hexane-ethyl acetate); 67% yield (Found: C, 81.0; H, 6.6.  $\text{C}_{17}\text{H}_{16}\text{O}_2$  requires C, 80.9; H, 6.4%); IR (nujol): 3400 (OH), 1750 ( $\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  9.05 (1H, bs, —OH), 7.86 (1H, dd,  $J=7, 2$  Hz, Ar—H), 7.2–7.6 (8H, m, Ar—H), 3.2 (1H, ddq,  $J=1, 3, 7$  Hz,  $\text{CH}_2$ —CH— $\text{CH}_3$ ), 2.42 (2H, m, CH— $\text{CH}_2$ —CO), 0.75 (3H, d,  $J=7$  Hz, CH— $\text{CH}_3$ ).

#### Acidic hydrolysis of **7**: Formation of **9**

Compound **7** (1 mmol) in toluene (15 ml) was refluxed for 2 hr in the presence of *p*-toluenesulphonic

acid (30 mg). Toluene was removed, water (10 ml) added to the residue, extracted with ether and the ether layer washed with aq. bicarbonate (10%), dried and evaporated to give **9**, m.p. 113–16° (ethanol), 77% yield (Found: C, 86.8; H, 6.5.  $C_{17}H_{14}O$  requires C, 87.2; H, 6.0%); IR (nujol): 3370 (OH)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  8.16 (1H, *dd*,  $J = 8$ , 2 Hz, Ar-H), 7.1–7.5 (8H, *m*, 8  $\times$  Ar-H), 6.7 (1H, *s*, Ar-H), 5.0–5.6 (1H, *b*, —OH), 2.15 (3H, *s*, Ar-CH<sub>3</sub>).

*Methanolysis of 7: Formation of 2-carbomethoxy-3-methyl-4-hydroxy-1-phenylnaphthalene (10)*

Through a solution of **7** (1 mmol) in methanol (25 ml) HCl gas was bubbled. After 20 min a white solid started separating out. HCl gas was bubbled further 30 min. The solid was filtered to give **10**, m.p. 145° (ethanol), 91% yield (Found: C, 77.8; H, 5.6.  $C_{19}H_{16}O_3$  requires C, 78.1; H, 5.5%); IR (nujol): 1670 (COOMe)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  12.35 (1H, *s*, —OH), 8.42 (1H, *dd*,  $J = 7$ , 3 Hz, Ar-H), 7.1–7.5 (8H, *m*, 8  $\times$  Ar-H), 3.98 (3H, *s*, COOMe), 2.33 (3H, *s*, Ar-CH<sub>3</sub>).

*Methanolysis of 11*

Methanolysis as above gave **3a**, m.p. 143° (hexane-ethyl acetate); 86% yield; identical with an authentic sample (IR and PMR).

*Treatment of phthalide (1b) with LDA and ClSiMe<sub>3</sub> and reaction with dienophiles*

The phthalide (**1b**) was treated with LDA and ClSiMe<sub>3</sub> as mentioned earlier at 0° and reacted with dienophiles.

(i) *Reaction with methyl acrylate. Formation of 12*

The above reaction led to **12**, m.p. 143° (hexane-ethyl acetate), 66% yield (Found: C, 69.8; H, 5.6.  $C_{19}H_{18}O_5$  requires C, 69.9; H, 5.6%); IR (nujol): 3500 (OH), 1660 (COOMe)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  12.3 (1H, *s*, —OH), 7.8 (1H, *dd*,  $J = 6$ , 2 Hz, Ar-H), 7.1–7.4 (5H, *m*, 5  $\times$  Ar-H), 6.7–6.8 (2H, *m*, 2  $\times$  Ar-H), 3.7 (6H, *s*, 2  $\times$  OCH<sub>3</sub>), 3.0, 3.2 (2H, *2d*,  $J = 14$  Hz each, C=C—CH<sub>2</sub>), 2.6–2.9 (1H, *b*, —OH).

(ii) *Reaction with methyl crotonate. Formation of 13*

Chromatography over silica gel using dichloromethane as eluent gave **13**, m.p. 105° (hexane-benzene), 56% yield (Found: C, 74.8; H, 5.2.  $C_{34}H_{28}O_7$  requires C, 74.4; H, 5.1%); IR (nujol): 1770 (lactone CO); 1750 (lactone-CO); 1690 (CO)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  7.8–8.1 (2H, *m*, 2  $\times$  Ar-H), 6.8–7.7 (14H, *m*, 14  $\times$  Ar-H), 6.35 (1H, *s*, Ar<sub>2</sub>CH—O), 3.76, 3.7 (6H, 2*s*, 2  $\times$  OMe), 3.67 (1H, *d*,  $J = 2$  Hz, —CO—CH—CH), 3.26 (1H, *dq*,  $J = 2$ , 7 Hz, CH<sub>3</sub>—CH—CH), 1.25 (3H, *d*,  $J = 7$  Hz, —CH—CH<sub>3</sub>).

(iii) *Reaction with maleic anhydride. Formation of 15*

This reaction led to **15**, m.p. 253° (dichloromethane), 58% yield (Found: C, 71.4; H, 3.9.  $C_{19}H_{12}O_5$  requires C, 71.3; H, 3.8%); IR (nujol): 1820 (C=O), 1750 (C=O)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  8.4–8.7 (1H, *m*, Ar—H), 6.9–7.8 (7H, *m*, 7  $\times$  Ar—H), 4.8–5.2 (1H, *b*, —OH), 3.85 (3H, *s*, —OCH<sub>3</sub>).

(iv) *Reaction with dimethyl fumarate, 2,3-Dicarbomethoxy-4-hydroxy-1-anisyl-naphthalene (3b)*

The reaction led to **3b**, m.p. 114° (ethanol), 56% yield (Found: C, 68.6; H, 4.9.  $C_{21}H_{17}O_6$  requires C, 68.8; H, 4.9%); IR (nujol): 1740 (COOMe), 1665 (COOMe)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  12.2 (1H, *s*, —OH), 8.4 (1H, *dd*,  $J = 7$ , 1.5 Hz, Ar-H), 7.1–7.5 (7H, *m*, 7  $\times$  Ar-H), 3.9, 3.75, 3.51 (9H, 3*s*, 3  $\times$  OMe).

*Basic hydrolysis of 13: Formation of 3-anisylphthalide (1b) and 14*

To a solution of **13** (1 mmol) in ethanol (10 ml) was added ethanolic potassium hydroxide (10%, 15 ml). The red homogeneous solution was stirred at room temperature for 10 hr. Work-up as described in the case of **7** gave **1b**, m.p. 113–14° (ethanol-hexane), 83% yield, identical (m.m.p., IR) with an authentic sample.

The bicarbonate washing was acidified with hydrochloric acid (2 *N*) and extracted with ether. The ether layer after drying and evaporation gave **14**, m.p. 88–89° (benzene-hexane), 79% yield (Found: C, 76.3; H, 6.4.  $C_{18}H_{18}O_3$  requires C, 76.6; H, 6.4%); IR (nujol): 3400 (OH), 1765 (C=O)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  8.8 (1H, *bs*, —OH), 7.1 (1H, *dd*,  $J = 7$ , 2 Hz, Ar-H), 7.2–7.6 (5H, *m*, 5  $\times$  Ar-H), 6.7–6.8 (2H, *m*, 2  $\times$  Ar-H), 3.75 (3H, *s*, —OCH<sub>3</sub>), 3.15 (1H, *ddq*,  $J = 1.5$ , 3 and 7 Hz, CH<sub>2</sub>—CH—CH<sub>3</sub>), 2.42 (2H, *m*, CH—CH<sub>2</sub>—CO), 0.72 (3H, *d*,  $J = 7$  Hz, CH—CH<sub>3</sub>).

*Methanolysis of 15: Formation of 2,3-dicarbomethoxy-4-hydroxy-1-anisyl-naphthalene (3b)*

Methanolysis, according to procedure mentioned earlier, gave **3b**, m.p. 114° (ethanol), 81% yield; its IR and PMR spectra were identical with an authentic sample.

*Naphthalenic Lignan lactone (4a): (i) Reduction of anhydride (11)*

To a solution of **11** in DMF (5 ml) was added sodium borohydride (0.5 g). The resulting green fluorescent solution was stirred at room temperature for 3 hr, acidified with hydrochloric acid (2 *N*) and extracted with ether. The ether layer was dried and evaporated to give the naphthalenic lignan lactone (**4a**), m.p. 174° (ethanol), 70% yield (Found: C, 78.4; H, 4.3.  $C_{18}H_{12}O_3$  requires C, 78.3; H, 4.4); IR (nujol): 3400

(OH), 1740 (C=O)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$  + DMSO- $d_6$ ):  $\delta$  8.3 (1H, *dd*,  $J=6, 2$  Hz, Ar-H), 7.2-7.7 (8H, *m*,  $8 \times$  Ar-H), 6.4-7.1 (1H, *b*, —OH), 5.25 (2H, *s*, Ar- $\text{CH}_2$ —O).

(ii) *Reduction of diester (3a)*

Similar reduction of **3a** gave the naphthalenic lignan lactone (**4a**), m.p. 174°, identical with the sample obtained above.

*Naphthalenic lignan lactone (4b): (i) Reduction of anhydride (15)*

The reduction of **15** was carried out as in the case **11**, to give **4b**, m.p. 179° (ethanol), 67% yield (Found: C, 74.7; H, 4.6.  $\text{C}_{19}\text{H}_{14}\text{O}_4$  requires C, 74.5; H, 4.6%); IR (nujol): 3390 (OH); 1730 (C=O)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$  + DMSO- $d_6$ ):  $\delta$  8.3 (1H, *dd*,  $J=6, 2$  Hz, Ar-H), 7.2-7.8 (7H, *m*, Ar-H), 6.0-7.0 (1H, *b*, —OH), 5.23 (2H, *s*, Ar- $\text{CH}_2$ —O), 3.9 (3H, *s*, —OMe).

(ii) *Reduction of diester (3b): Formation of 4b*

Similar reduction of **3b** gave **4b**, m.p. 179°, identical (m.m.p., IR, PMR) with the sample obtained above.

**Hydroxyacetal (17)**

To a solution of bromoacetal **16** (10 mmol) in THF (20 ml) was added *n*-BuLi in ether (11 mmol) at  $-78^\circ$ . After 15 min a solution of trimethoxybenzaldehyde (11 mmol) in THF (20 ml) was added. After being stirred for 30 min at  $-78^\circ$  the reaction mixture was decomposed with water (10 ml) and THF removed *in vacuo*. The aqueous layer was extracted with ether. Drying and evaporation of solvent gave **17**, 78% yield, which was not rigorously purified due to instability; IR (nujol): 3440 (OH)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  7.08 (1H, *s*, Ar-H), 6.97 (1H, *s*, Ar-H), 6.99 (2H, *s*,  $2 \times$  Ar-H), 6.1 (1H, *d*,  $J=3$  Hz, —CH—OH), 6.0 (1H, *s*, O—CH—O), 5.95 (2H, *s*, O— $\text{CH}_2$ —O), 4.11 (4H, *m*, O— $\text{CH}_2$ — $\text{CH}_2$ —O), 3.87, 3.86, 3.85 (9H, *3s*, 3Ar-OCH<sub>3</sub>), 3.4 (1H, *d*,  $J=3$  Hz, —OH).

**Phthalide (1c)**

A solution of **17** (10 mmol) in benzene (60 ml) was vigorously stirred with  $\text{H}_2\text{SO}_4$  (2 N, 120 ml) for 1 hr. To this mixture sodium dichromate (7 g) was added and stirred further for 3 hr. The benzene layer was separated and the acidic layer extracted with benzene. The combined benzene layer, after drying and evaporation, gave a thick residue. To this methanol (20 ml) was added. On keeping for 12 hr, **1c** was obtained,

m.p. 218° (methanol), 55% yield (Found: C, 62.6; H, 4.7.  $\text{C}_{18}\text{H}_{16}\text{O}_7$  requires C, 62.8; H, 4.7%); IR (nujol): 1760 (C=O)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (1H, *s*, Ar-H); 6.7 (1H, *s*, Ar-H), 6.4 (2H, *s*, Ar-H); 6.1 (3H, *s*, CH and O— $\text{CH}_2$ —O overlapping); 3.9 (9H, *s*,  $3 \times$  OMe).

*Treatment of phthalide (1c) with LDA and ClSiMe<sub>3</sub> and reaction with dimethyl fumarate*

Reaction of **1c** with LDA and ClSiMe<sub>3</sub> was carried out as mentioned earlier, but at  $-78^\circ$ , to give 2, 3-dicarbomethoxy-4-hydroxy-1-(3, 4, 5-trimethoxyphenyl) naphthalene (**3c**), m.p. 241-42° (ethanol-ethyl acetate), 20% yield (Found: C, 61.4; H, 4.6.  $\text{C}_{24}\text{H}_{22}\text{O}_{10}$  requires C, 61.3; H, 4.7%); IR (nujol): 1740 (COOMe), 1665 (COOMe)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  12.2 (1H, *s*, —OH), 7.7 (1H, *s*, Ar—H), 6.84 (1H, *s*, Ar-H), 6.36 (2H, *s*, Ar-H), 6.1 (2H, *s*, O— $\text{CH}_2$ —O), 4.0, 3.9, 3.6 (15H, *3s*,  $5 \times$  OMe).

*Tetradehydropodophyllotoxin (4c): Reduction of 3c*

The naphthalenic diester (**3c**, 0.25 mmol) was dissolved in methanol (70 ml) and to this NaBH<sub>4</sub> (0.5 g) was added. The reaction mixture was stirred for 3 hr during which two further lots of NaBH<sub>4</sub> (0.5 g each) were added at the end of every hour. Methanol was removed *in vacuo* and the residue treated with hydrochloric acid (2N, 20 ml). The acidic layer was extracted with dichloromethane to give **4c**, m.p. 269° (dichloromethane) (lit.<sup>7</sup> m.p. 270°), 80% yield; IR (nujol): 3400 (OH), 1750 (C=O)  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$  + DMSO- $d_6$ ):  $\delta$  7.4 (1H, *s*, Ar-H), 6.7 (1H, *s*, Ar-H), 6.3 (2H, *s*,  $2 \times$  Ar-H), 5.9 (2H, *s*, O— $\text{CH}_2$ —O), 5.3 (2H, *s*, Ar- $\text{CH}_2$ —O), 3.8 (9H, *s*,  $3 \times$  OMe).

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## Studies in Synthesis of Xanthone Derivatives: Part VI — Synthesis of Furano- & Difurano-xanthenes

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2-Methylresorcinol, resorcinol and 5-methylresorcinol on thermal condensation with methyl 2,4-dihydroxybenzoate in diphenyl ether afford 3,6-dihydroxy-4-methylxanthone (I), 3,6-dihydroxyxanthone (VII) and 1,6-dihydroxy-3-methylxanthone (XII), respectively. I, VII and XII on allylation, Claisen migration, cyclisation with sulphuric acid and dehydrogenation with palladised charcoal give 2,9,11-trimethyldifuro[3,2-*b*:3',2'-*h*]xanthen-6(*H*)-one (VI), 2,10-dimethyldifuro[2,3-*c*:3',2'-*h*]xanthen-6(*H*)-one (XI) and 7-hydroxy-2,9-dimethyldifuro[2,3-*c*]xanthen-6(*H*)-one (XVI), respectively. Structures of final and intermediate products have been established by PMR spectral data.

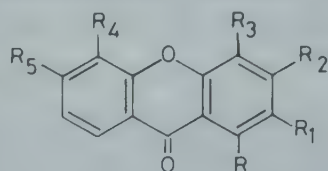
In continuation of our work on the synthesis of furanoxanthenes<sup>1-3</sup>, we wish to report here the synthesis of two new difuranoxanthone 2,9,11-trimethyldifuro[3,2-*b*:3',2'-*h*]xanthen-6(*H*)-one (VI) and 2,10-dimethyldifuro[2,3-*c*:3',2'-*h*]xanthen-6(*H*)-one (XI), and one new furanoxanthone 7-hydroxy-2,9-dimethyldifuro[2,3-*c*]xanthen-6(*H*)-one (XVI) starting from 3,6-dihydroxy-4-methylxanthone (I), 3,6-dihydroxyxanthone (VII) and 1,6-dihydroxy-3-methylxanthone (XII), respectively.

Methyl 2,4-dihydroxybenzoate on thermal condensation<sup>4,5</sup> with 2-methylresorcinol in diphenyl ether afforded 3,6-dihydroxy-4-methylxanthone (I), the structure of which was established by preparing its diacetyl derivative (II) and from its IR spectrum. The xanthone I on allylation followed by Claisen migration gave 2,5-diallyl derivative (IV) which on cyclisation with conc. sulphuric acid<sup>6</sup> yielded 2,9,11-trimethyl-1,2,8,9-tetrahydrodifuro[3,2-*b*:3',2'-*h*]xanthen-6(*H*)-one (V). Its structure was established by PMR spectrum (CDCl<sub>3</sub>) which exhibited

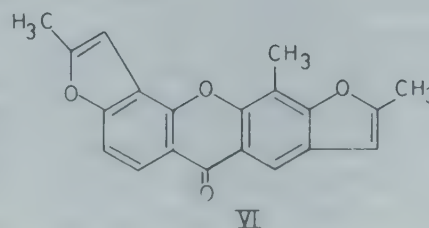
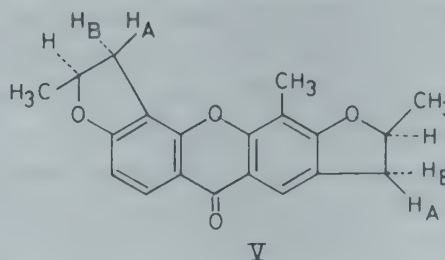
signals at  $\delta$  1.52 (3H, *d*,  $J=7$  Hz,  $-\text{CH}_3$  at C-2), 1.58 (3H, *d*,  $J=7$  Hz,  $-\text{CH}_3$  at C-9), 2.31 (3H, *s*,  $-\text{CH}_3$  C-11), 2.95 (2H, *q*,  $J_{1(A),1(B)}=J_{8(A),8(B)}=16$  Hz,  $J_{8(A),9}=J_{1(A),2}=J_{trans}=8$  Hz,  $H_A$  at C-1 and C-8), 3.48 (2H, *q*,  $J_{1(A),1(B)}=J_{8(A),8(B)}=16$  Hz,  $J_{1(B),2}=J_{8(B),9}=J_{cis}=9$  Hz,  $H_B$  at C-1 and C-8), 5.12 (2H, *m*, methine protons at C-2 at C-9), 6.78 (1H, *d*,  $J=9$  Hz, H-4), 7.97 (1H, *s*, H-7), 8.18 (1H, *d*,  $J=9$  Hz, H-5).

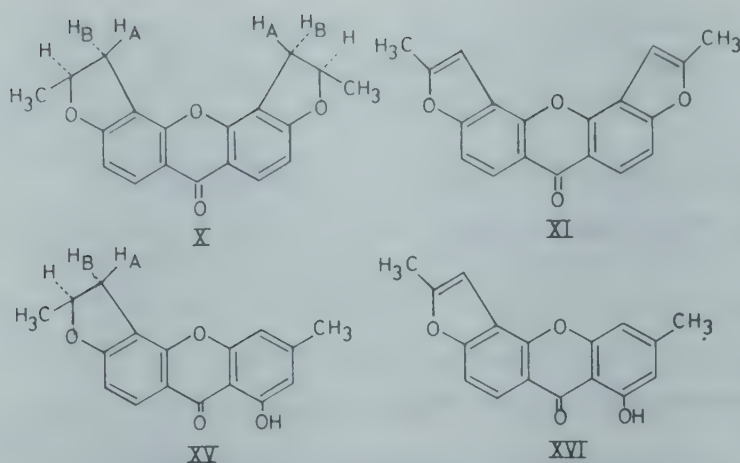
The coupling constant for *cis*-hydrogen is greater than *trans*-hydrogen in the case of 2,3-dihydrobenzofuran derivatives<sup>7</sup>. Compound IV, on dehydrogenation with palladised charcoal (10%) gave VI.

Methyl  $\beta$ -resorcyate on condensation with resorcinol in diphenyl ether afforded 3,6-dihydroxyxanthone (VII), which on allylation with allyl bromide in the presence of potassium carbonate in boiling acetone gave 3,6-allyloxyxanthone (VIII). The structure of VIII was established by PMR spectrum and conversion into 4,5-diallyl-3,6-dihydroxyxanthone (IX) by Claisen migration in dimethylaniline. The PMR spectrum of the acetoxy derivative (IXa) of IX in



- I  $R=R_1=R_4=H, R_2=R_5=OH, R_3=CH_3$
- II  $R=R_1=R_4=H, R_2=R_5=OCOCH_3, R_3=CH_3$
- III  $R=R_1=R_4=H, R_2=R_5=OCH_2CH=CH_2, R_3=CH_3$
- IV  $R=H, R_1=R_4=CH_2CH=CH_2, R_2=R_5=OH, R_3=CH_3$
- VII  $R=R_1=R_3=R_4=H, R_2=R_5=OH$
- VIII  $R=R_1=R_3=R_4=H, R_2=R_5=OCH_2CH=CH_2$
- IX  $R=R_1=H, R_3=R_4=CH_2CH=CH_2, R_2=R_5=OH$
- XII  $R=R_5=OH, R_2=CH_3, R_1=R_3=R_4=H$
- XIII  $R=OH, R_5=OCH_2CH=CH_2, R_2=CH_3, R_1=R_3=R_4=H$
- XIV  $R=R_5=OH, R_2=CH_3, R_1=R_3=H, R_4=CH_2CH=CH_2$





$\text{CDCl}_3$  exhibited two doublets each integrating for two protons having  $J$  value of 9 Hz, one at  $\delta$  8.2 due to H-1 and H-8 and the other at 7.2 due to H-2 and H-7, indicating that the migrated allyl groups occupy positions 4 and 5. Compound IX when treated with conc.  $\text{H}_2\text{SO}_4$  underwent cyclization to give 2,10-dimethyl-1, 2, 10, 11-tetrahydrodifuro[2, 3-*c*: 3', 2'-*h*]xanthen-6(*H*)-one (X). Its structure was established on the basis of PMR data in  $\text{CDCl}_3$ . The compound X on dehydrogenation with palladised charcoal (10%) gave XI. The PMR spectrum of which in  $\text{CDCl}_3$  displayed a singlet due two methyl groups at  $\delta$  2.49, a singlet of two-proton intensity at 6.62 assignable for H-1 and H-11 and other signals in the aromatic region compatible with the structure XI. The compound XI was also obtained when IXa was cyclised by the method of Adams and Rindfuz<sup>8</sup>.

Methyl  $\beta$ -resorcyate on thermal condensation with 5-methylresorcinol in boiling diphenyl ether gave 1,6-dihydroxy-3-methylxanthone (XII), the structure of which was established on the basis of PMR data of its acetoxy derivative. Treatment of XII with allyl bromide in the usual manner afforded the allyl derivative (XIII) which gave green colour with ethanolic ferric chloride suggesting the presence of a hydroxy group in XIII. 6-Allyloxy-1-hydroxyxanthone (XIII) on Claisen migration in dimethylaniline gave 5-allyl-1,6-dihydroxyxanthone (XIV), which on treatment with conc.  $\text{H}_2\text{SO}_4$  gave 7-hydroxy-2,9-dimethyl-1,2-dihydrofuro[2,3-*c*]xanthen-6(*H*)-one (XV). The PMR spectrum of XV in  $\text{CDCl}_3$  exhibited a three-proton doublet ( $J=6$  Hz) at  $\delta$  1.55 due to methyl group at position-2, a quartet at 2.92 (1H,  $J_{1(A), 1(B)}=16$  Hz,  $J_{1(A), 2}=J_{trans}=8$  Hz) due to  $\text{H}_A$  at C-1 and another quartet at 3.5 (1H,  $J_{1(A), 1(B)}=16$  Hz,  $J_{1(B), 2}=J_{cis}=9$  Hz) due to the proton  $\text{H}_B$  at C-1. Compound XV on dehydrogenation with palladised charcoal (10%) afforded XVI. Its structure was established by PMR ( $\text{CDCl}_3$ ) spectrum exhibiting a three-proton singlet at  $\delta$  2.55 due to the methyl group at position-2, an-

other three-proton singlet at 2.45 due to the methyl group at position-9, a doublet at 8.05 (1H,  $J=9$  Hz) for H-5, a doublet at 7.35 (1H,  $J=9$  Hz) for H-4, a singlet at 6.72 (2H) for H-1 and H-10, a singlet at 6.6 for H-8, and a singlet at 12.65 due to  $-\text{OH}$  at C-7.

### Experimental Procedure

PMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrophotometer using TMS as an internal standard (chemical shifts in  $\delta$ , ppm) and IR spectra on a Beckman IR-20 spectrophotometer ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ).

#### 3,6-Dihydroxy-4-methylxanthone (I)

A mixture of 2-methylresorcinol (6.2 g; 0.05 mol), methyl 2,4-dihydroxybenzoate (8.4 g; 0.05 mol) and diphenyl ether (15 ml) was refluxed for 13-16 hr and subjected to steam distillation to remove diphenyl ether. The residue was washed with saturated sodium bicarbonate solution (50 ml) and dissolved in aq. sodium bicarbonate (8%; 80 ml), filtered and acidified. The separated product was filtered, washed with water, dried and crystallized from acetic acid to give I, m.p.  $> 325^\circ$ , yield 3.5 g (Found: C, 69.8; H, 4.4.  $\text{C}_{14}\text{H}_{10}\text{O}_4$  requires C, 69.4; H, 4.1%); IR (KBr): 1646 ( $\gamma$ -pyronyl  $> \text{C}=\text{O}$ ), 3280 (phenolic  $-\text{OH}$ ).

The diacetyl derivative (II) was prepared by heating a mixture of I (1 g), acetic anhydride (8 ml) and pyridine (0.3 ml) on a water-bath for 6 hr and crystallised from benzene as colourless needles, m.p.  $194^\circ$ , yield 0.7 g (Found: C, 66.6; H, 4.2.  $\text{C}_{18}\text{H}_{14}\text{O}_6$  requires C, 66.3; H, 4.3%); IR (KBr): 1658 ( $\gamma$ -pyronyl  $> \text{C}=\text{O}$ ), 1745 ( $-\text{OCOCH}_3$ ).

#### 3,6-Diallyloxy-4-methylxanthone (III)

A mixture of I (2.5 g), allyl bromide (3.2 g) and anhyd.  $\text{K}_2\text{CO}_3$  (8 g) was refluxed in dry acetone (400 ml) on a water-bath for 20 hr, poured into water and the separated product filtered, washed with dil. NaOH solution, and crystallised from benzene-pet. ether as colourless long needles, m.p.  $128^\circ$  yield 2.2 g (Found: C, 74.2; H, 5.4.  $\text{C}_{20}\text{H}_{18}\text{O}_4$  requires C, 74.5; H, 5.6%).

#### 2,5-Diallyl-3,6-dihydroxy-4-methylxanthone (IV)

Compound III (1.8 g) was refluxed with dimethylaniline (10 ml) for 7 hr. The reaction mixture was cooled, poured into cold dil. HCl and the separated product recrystallised from ethanol as small prisms, m.p.  $221^\circ$ , yield 1.2 g (Found: C, 74.9; H, 5.5.  $\text{C}_{20}\text{H}_{18}\text{O}_4$  requires C, 74.5; H, 5.6%); IR (KBr): 1642 ( $\gamma$ -pyronyl  $> \text{C}=\text{O}$ ), 3160 (phenolic  $-\text{OH}$ ).

#### 2,9,11-Trimethyl-1,2,8,9-tetrahydrodifuro[3,2-*b*: 3'2'-*h*]xanthen-6(*H*)-one (V)

A solution of IV (0.8 g) in  $\text{H}_2\text{SO}_4$  (85%; 7 ml) was

heated in a water-bath for 15 min at 75° and the reaction mixture poured onto crushed ice. The crude product thus obtained was chromatographed over silica gel using pet. ether-benzene (1:4) as eluant and crystallised from benzene-pet. ether as colourless shining needles, m.p. 198-99°, yield 0.55 g (Found: C, 75.0; H, 5.8. C<sub>20</sub>H<sub>18</sub>O<sub>4</sub> requires C, 74.5; H, 5.6%).

*2,9,11-Trimethyldifuro[3,2-b:3',2'-h]xanthen-6(H)-one (VI)*

A mixture of (IV) (0.5 g), palladised charcoal (10%, 0.9 g) and diphenyl ether (10 ml) was refluxed for 10 hr. The reaction mixture was filtered hot and diphenyl ether removed by steam distillation. The product was chromatographed on silica gel, using benzene-chloroform (2:3) as eluant to give VI, which crystallised from acetic acid, m.p. 254°, yield 0.2 g (Found: C, 75.4; H, 4.8. C<sub>20</sub>H<sub>14</sub>O<sub>4</sub> requires C, 75.3; H, 4.4%); IR (KBr): 1648 (γ-pyrone >C=O), 842 (furan rings).

*3,6-Dihydroxyxanthone (VII)*

A mixture of resorcinol (2.2 g, 0.02 mol), methyl β-resorcilate (3.5 g, 0.02 mol) and diphenyl ether (10 ml) was refluxed for 10 hr and the reaction mixture worked-up as usual to give a solid which on crystallisation from aq. ethanol furnished VII m.p. 320° (lit.<sup>8</sup>, m.p. 330°), yield 2.2 g (Found: C, 68.9; H, 3.8. C<sub>13</sub>H<sub>8</sub>O<sub>4</sub> requires C, 68.4; H, 3.5%).

*3,6-Diallyloxyxanthone (VIII)*

A mixture of VII (2 g), allyl bromide (3 ml) and anhyd. K<sub>2</sub>CO<sub>3</sub> (5 g) was refluxed in dry acetone (100 ml) for 12 hr, and the reaction mixture worked-up as usual to give VIII which crystallised from ethanol, m.p. 140° (Found: C, 74.2; H, 5.3. C<sub>19</sub>H<sub>16</sub>O<sub>4</sub> requires C, 74.0; H, 5.2%); PMR (CDCl<sub>3</sub>): 8.15 (*d*, 2H, *J*=9 Hz, H-1 and H-8), 7.0-6.65 (*m*, 4H, H-2, H-4, H-5 and H-6), 6.0 (*m*, 2H, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.35 (*m*, 4H, 2 × CH<sub>2</sub> CH=CH<sub>2</sub>), 4.6 (*m*, 4H, 2 × CH<sub>2</sub>CH=CH<sub>2</sub>).

*4,5-Diallyl-3,6-dihydroxyxanthone (IX)*

Compound VIII (2.0 g) was refluxed in dimethylaniline (10 ml) for 6 hr and the reaction mixture on usual work-up gave a solid product which crystallised from aq. ethanol, m.p. 222° (Found: C, 73.7; H, 5.0. C<sub>19</sub>H<sub>16</sub>O<sub>4</sub> requires C, 74.0; H, 5.2%); acetate (Ac<sub>2</sub>O/pyridine): m.p. 160° (Found: C, 70.6; H, 5.0. C<sub>23</sub>H<sub>20</sub>O<sub>6</sub> requires C, 70.4; H, 5.1%); PMR (CDCl<sub>3</sub>): 8.2 (*d*, 2H, *J*=9 Hz, H-1 and H-8), 7.2 (*d*, 2H, *J*=9 Hz, H-2 and H-7), 6.1-5.7 (*m*, 2H, 2 × -CH<sub>2</sub>CH=CH<sub>2</sub>), 5.15-4.9 (*m*, 4H, 2 × -CH<sub>2</sub>CH=CH<sub>2</sub>), 3.6 (*d*, 4H, *J*=9 Hz, 2 × -CH<sub>2</sub>CH=CH<sub>2</sub>), 2.35 (*s*, 6H, 2 × -OCOCH<sub>3</sub>).

*2,10-Dimethyl-1,2,10,11-tetrahydrofuro[2,3-c:3',2'-h]xanthen-6(H)-one (X)*

A solution of IX (0.6 g) in H<sub>2</sub>SO<sub>4</sub> was heated in a water-bath for 15 min, and the reaction mixture worked-up as above to give a solid product which on crystallisation from ethanol afforded X, m.p. 180° (Found: C, 73.8; H, 5.6. H<sub>19</sub>H<sub>16</sub>O<sub>4</sub> requires C, 74.0; H, 5.2%); PMR (CDCl<sub>3</sub>): 8.08 (*d*, 2H, *J*=9 Hz, H-5 and H-7), 6.7 (*d*, 2H, *J*=9 Hz, H-4 and H-8), 5.1 (*m*, 2H, H-2 and H-10), 3.4 (*q*, 2H, *J*<sub>1(A),1(B)</sub>=*J*<sub>11(A)</sub>, *J*<sub>11(B)</sub>=16 Hz, *J*<sub>1(B),2</sub>=*J*<sub>11(B),10</sub>=*J*<sub>cis</sub>=8.5 Hz, H<sub>B</sub> protons at C-1 and C-11), 2.78 (*q*, 2H, *J*<sub>1(A),1(B)</sub>=*J*<sub>11(A),11(B)</sub>=16 Hz, *J*<sub>1(A),2</sub>=*J*<sub>11(A),10</sub> *J*<sub>trans</sub>=8 Hz, H<sub>A</sub> protons at C-1 and C-11), 1.65 (*d*, 6H, *J*=6 Hz 2 × -CH<sub>3</sub>).

*2,10-Dimethyldifuro[2,3-c:3'2'-h]xanthen-6(H)-one (XI)*

A mixture of X (0.3 g), palladised charcoal (10%, 0.5 g) and diphenyl ether was refluxed for 10 hr and the reaction mixture worked-up as described before. The product was crystallised from aq. acetic acid, m.p. 256-59°; PMR (CDCl<sub>3</sub>): 8.2 (*d*, 2H, *J*=9 Hz, H-5 and H-7), 7.3 (*d*, 2H, *J*=9 Hz, H-4 and H-8), 6.62 (*s*, 2H, H-2 and H-11), 2.49 (*s*, 6H, 2 × -CH<sub>3</sub>).

*1,6-Dihydroxy-3-methylxanthone (XII)*

A mixture of orcinol (1.4 g, 0.01 mol), methyl β-resorcilate (1.7 g, 0.01 mol) and diphenyl ether (5 ml) was refluxed for 8 hr, and diphenyl ether steam distilled to give the crude product (1.3 g) which on column chromatography over silica gel using benzene as eluant gave XII (800 mg), m.p. 315° (lit.<sup>9</sup>, m.p. 326°) (Found: C, 69.0; H, 4.6. C<sub>14</sub>H<sub>10</sub>O<sub>4</sub> requires C, 69.4; H, 4.1%); acetate (Ac<sub>2</sub>O/pyridine): m.p. 165° (lit.<sup>8</sup>, m.p. 161°) (Found: C, 66.3; H, 4.5. C<sub>18</sub>H<sub>10</sub>O<sub>4</sub> requires C, 66.3; H, 4.3%); PMR (CDCl<sub>3</sub>): 8.25 (*d*, 1H, *J*=9 Hz, H-8), 7.3-7.18 (*m*, 3H, H-4, H-5 and H-7), 6.82 (*d*, 1H, *J*=1 Hz, H-2), 2.5 (*s*, 3H, Ar-CH<sub>3</sub>), 2.46 (*s*, 3H, -OCOCH<sub>3</sub>), 2.35 (*s*, 3H, -OCOCH<sub>3</sub>).

*6-Allyloxy-3-methyl-1-hydroxyxanthone (XIII)*

A mixture of XII (2.0 g), allyl bromide (3.0 ml) and anhyd. K<sub>2</sub>CO<sub>3</sub> (6 g) was refluxed in dry acetone (200 ml) in a water-bath for 20 hr, and the reaction mixture worked-up as usual to give XIII which crystallised from ethyl acetate, m.p. 176° (Found: C, 71.9; H, 4.5. C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> requires C, 72.4; H, 4.9%).

*5-Allyl-3-methyl-1,6-dihydroxyxanthone (XIV)*

Compound XIII (2.0 g) was refluxed in dimethylaniline (10 ml) for 10 hr and the reaction mixture worked-up as usual. The product was crystallised from acetic acid to give XIV as yellow needles, m.p. 240° (Found: C, 72.9; H, 5.3. C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> requires C, 72.4; H, 4.9%).

73.3; H, 4.9%); acetate ( $\text{AC}_2\text{O}$ /pyridine): m.p.  $155^\circ$  (Found: C, 69.8; H, 5.4.  $\text{C}_{19}\text{H}_{16}\text{O}_5$  requires C, 70.4; H, 4.9%); PMR ( $\text{CDCl}_3$ ): 8.05 (*d*, 1H,  $J=9$  Hz, H-8), 7.0 (*d*, 1H,  $J=9$  Hz, H-7), 7.08 (*s*, 1H, H-4), 6.7 (*s*, 1H, H-2), 5.6-6.1 (*m*, 1H,  $-\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.0 (*m*, 2H,  $-\text{CH}_2\text{CH}=\text{CH}_2$ ), 3.5 (*d*, 2H,  $J=7$  Hz,  $\text{CH}_2-\text{CH}=\text{CH}_2$ ), 2.4 (*s*, 3H, Ar- $\text{CH}_3$ ), 2.28 (*s*, 3H,  $-\text{OCOCH}_3$ ).

**7-Hydroxy-2,9-dimethyl-1,2-dihydrofuro[2,3-*c*]xanthen-6(*H*)-one (XV)**

Compound XIV (0.5 g) was triturated with conc.  $\text{H}_2\text{SO}_4$  in a water-bath for 15 min and the reaction mixture worked-up as usual. The product crystallised from aq. acetic acid to give XV as a brown needles, m.p.  $160^\circ$  (Found: C, 71.8; H, 5.4.  $\text{C}_{17}\text{H}_{14}\text{O}_4$  requires C, 72.3; H, 4.90%); PMR ( $\text{CDCl}_3$ ): 8.0 (*d*, 1H,  $J=9$  Hz, H-5), 6.7 (*d*, 1H,  $J=9$  Hz, H-4), 6.55 (*s*, 1H, H-10), 6.49 (*s*, 1H, H-8), 5.15 (*m*, 1H, H-2), 3.5 (*q*, 1H,  $J=16, 9$  Hz, H-1), 2.92 (*q*, 1H,  $J=16, 8$  Hz, H-1), 2.38 (*s*, 3H,  $\text{CH}_3$  at C-9), 1.55 (*d*, 3H,  $J=7$  Hz,  $\text{CH}_3$  at C-2).

**2,9-Dimethyl-7-hydroxyfuro[2,3-*c*]xanthen-6(*H*)-one (XVI)**

A mixture of XV (0.2 g) palladised charcoal (10%,

0.5 g) and diphenyl ether (10 ml) was refluxed for 10 hr and the product isolated as usual and crystallised from aq. alcohol, m.p.  $195^\circ$  (Found: C, 72.6; H, 4.5.  $\text{C}_{17}\text{H}_{12}\text{O}_4$  requires C, 72.9; H, 4.3%).

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## Lactam & Amide Acetals: Part XVII—Reactions of 1,1-Dimethoxy-1-(N-piperidiny)ethane & 2-Ethoxy-1-methylindole with Electrophiles

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Reactions of araldehydes with 1,1-dimethoxy-1-(N-piperidiny)ethane (**1**) yield 3-aryl-4-(N-piperidiny)-2-propen-1-ones (**3-10**), while 2-ethoxy-1-methylindole (**2**) reacts with araldehydes to afford aryl-di-2-ethoxy-1-methylindole-2-ylmethanes (**11-16**). Reaction of **2** with phenyl isocyanate and phenyl isothiocyanate gives 2-ethoxy-1-methyl-3-phenylcarbamoyl and thiocarbamoylindoles (**17** and **18**) respectively.

During our earlier work<sup>1-4</sup> on the reactions of lactam acetals with electrophilic reagents, it was observed that product formation was governed by the reactivity of electrophiles and the ring size of lactams. As an extension we have presently studied the reactions of some newer types of lactam and amide acetals with electrophiles. Reactions of 2-ethoxyindole (**2**) which simulates the enamine species present in lactam acetals and 1,1-dimethoxy-1-(N-piperidiny)ethane (**1**)<sup>5</sup>, an amide acetal, with araldehydes, aryl isocyanates and aryl isothiocyanates have now been carried out and the results are described in this paper.

Compound (**1**)<sup>5</sup> reacted with benzaldehyde, *o*-chloro-, *o*-fluoro-, *o*-nitro-, *m*-chloro-, *p*-chloro-, *p*-nitrobenzaldehydes and *o*-tolualdehyde to form cinammamide derivatives **3-10** in 23-58% yields; large coupling constants ( $J = 16$  Hz) for 2-CH and 3-CH in **3-10** suggested *E*-geometry for these compounds (Chart 1).

2-Ethoxy-1-methylindole (**2**) reacted with benzaldehyde, *o*-nitro-, *p*-nitro-, *m*-chloro- and *p*-chloro-benzaldehydes to form aryl-diindolylmethanes (**11-16**), arising by the condensation of two molecules of **2** with one molecule of araldehyde. Indole derivatives have been shown to react with araldehydes under acid-catalysed conditions<sup>6</sup>, to give diindolylmethanes of the type **11-16**. Facile condensation of **2** with araldehydes under neutral and mild reaction conditions is presumably due to electron donation of C<sub>2</sub>-ethoxy substituent which enhances the nucleophilicity of C-3.

2-Ethoxyindole (**2**) reacted with phenyl isocyanate and phenyl isothiocyanate to give 3-phenylcarbamoyl/thiocarbamoyl derivatives **17** and **18** in which the ethoxy substituent at C-2 of the indole remained unaffected. This is in contrast to the reaction of 2,2-dimethoxy-1-methylpyrrolidine which reacted with

aryl isocyanates and aryl isothiocyanates yielding pyrrolopyrimidines<sup>4</sup> (Chart 1).

### Experimental Procedure

Melting points were determined in an electrically heated apparatus (Townson & Mercer, England) and are uncorrected. The compounds were routinely checked for homogeneity by TLC on silica gel plates. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer and PMR spectra on Varian EM-360L and Perkin-Elmer R-32 instruments using TMS as an internal standard.

#### General method for reaction of amide acetal (**1**) with araldehyde

*Method A*—A solution of **1** (0.01 mol) in anhydrous ether (5 ml) was added dropwise to a stirred solution of araldehyde (0.009 mol) in anhydrous ether (10 ml) and the stirring continued for 6 hr. The product which either separated directly from the reaction mixture or after concentration of the solvent, was filtered and crystallized.

*Method B*—A mixture of **1** (0.01 mol) and araldehyde (0.009 mol) was left at room temperature for 24-30 hr. The resulting mass was kept *in vacuo* to remove methanol generated during the reaction and triturated with hexane-ether to furnish the product which was crystallised from hexane-ether.

*Method C*—A mixture of **1** (0.01 mol) and araldehyde (0.009 mol) was heated at 80° for 12 hr. The methanol liberated during the reaction was removed *in vacuo*. The product was isolated by column chromatography on silica gel or florisil column using hexane-ethyl acetate as eluant.

Compounds **3-10** were synthesized by the above methods and their physical constants are given in Table 1. The spectral data of the representative **3**: IR(KBr): 2920, 1645, 1595, 1025, 860, 775 cm<sup>-1</sup>; PMR(CDCl<sub>3</sub>):  $\delta$ 1.30.1.78 (*m*, 6H, 3'-, 4'- and

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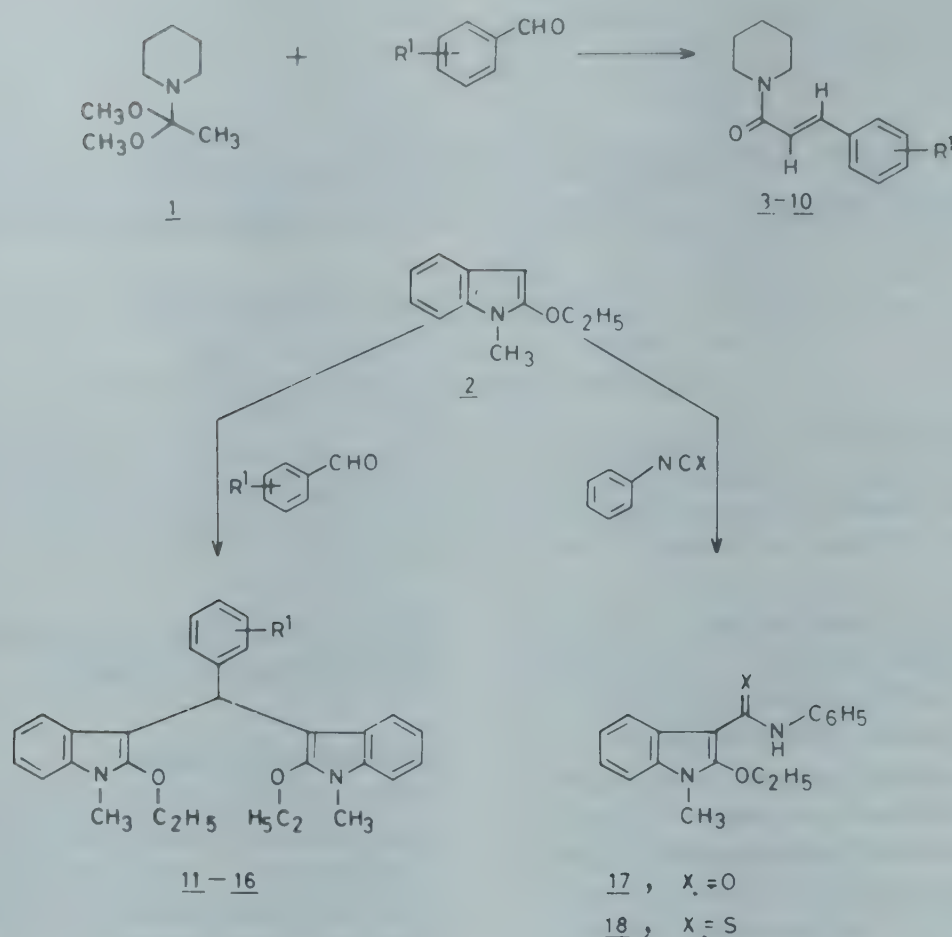


Table 1—Physical Data of 3-Aryl-1-(N-piperidiny)-2-propen-1-one (3-10)

Compound	R <sup>1</sup>	Method	m.p. °C	Yield %	Mol. formula* (M <sup>+</sup> )
3	H	A	110-14	52	C <sub>14</sub> H <sub>17</sub> NO (215.29)
4	<i>o</i> -Cl	B	104	45	C <sub>14</sub> H <sub>16</sub> NOCl (249.73)
5	<i>o</i> -F	B	88	48	C <sub>14</sub> H <sub>16</sub> NOF (233.29)
6	<i>o</i> -CH <sub>3</sub>	C	oil	57	C <sub>14</sub> H <sub>19</sub> NO (229.32)
7	<i>o</i> -NO <sub>2</sub>	B	87	23	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (260.29)
8	<i>m</i> -Cl	C	86	58	C <sub>14</sub> H <sub>16</sub> NOCl (249.73)
9	<i>p</i> -Cl	C	127	27	C <sub>14</sub> H <sub>16</sub> NOCl (249.73)
10	<i>p</i> -NO <sub>2</sub>	A	159-61	55	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (260.29)

\* C, H & N analyses of the compounds were within  $\pm 0.4\%$  of the calculated values.

5'—CH<sub>2</sub>), 3.32-3.65 (*m*, 4H, 2'- and 6'-CH<sub>2</sub>), 6.74 (*d*, 1H, 1—CH, *J*= 16 Hz), 7.01-7.40 (*m*, 5H, ArH) and 7.48 (*d*, 1H, 2-CH, *J*= 16 Hz).

*General method for reactions of 2-ethoxy-1-methylindole (2) with araldehydes*

A solution of **2** (0.02 mol) in anhydrous ether (5 ml)

Table 2—Physical Data of Aryldi-(2-ethoxy-1-methylindol-2-yl)methanes (11-16)

Compound	R <sup>1</sup>	m.p. °C	Yield %	Mol. formula* (M <sup>+</sup> )
11	H	153	69	C <sub>29</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> (438)
12	<i>o</i> -CH <sub>3</sub>	172-74	51	C <sub>30</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> (452)
13	<i>o</i> -NO <sub>2</sub>	219	63	C <sub>29</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> (483)
14	<i>m</i> -NO <sub>2</sub>	157-58	77	C <sub>29</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> (483)
15	<i>m</i> -Cl	122-25	48	C <sub>29</sub> H <sub>29</sub> N <sub>2</sub> O <sub>2</sub> Cl (472.5)
16	<i>p</i> -Cl	139	59	C <sub>29</sub> H <sub>29</sub> N <sub>2</sub> O <sub>2</sub> Cl

\*C, H & N analyses of the compounds were within  $\pm 0.35\%$  of the calculated values.

was added dropwise to a solution of araldehyde (0.009 mol) in anhydrous ether (10 ml) and stirred at room temperature for 4-12 hr. The product either separated out from the reaction mixture as a solid or was obtained by trituration with ether-hexane and was crystallised from methylene chloride-ether.

Compounds **11-16** were synthesized by the above method and their physical constants are given in Table 2. The spectral data of the representative compound **11**: IR(KBr): 3030, 2950, 1610, 1560, 1335, 1020, 870, 740 cm<sup>-1</sup>; PMR(CCl<sub>4</sub>):  $\delta$ 1.01 (*t*, 6H,

$2 \times \text{C}-\text{CH}_3$ ), 3.45 (*s*, 6H,  $2 \times \text{N}-\text{CH}_3$ ), 3.57 (*q*, 4H,  $2 \times \text{O}-\text{CH}_2$ ), 5.88 (*s*, 1H,  $\text{Ar}_3\text{CH}$ ) and 6.60-7.40 (*m*, 12H, ArH).

*Preparation of 2-ethoxy-1-methyl-3-phenylcarbamoyl and thiocarbamoylindoles (17 & 18)*

A mixture of **3** (1.0 mmol) and phenylisocyanate or isothiocyanate (1.1 mmol) in anhydrous benzene was heated under reflux for 10 hr. Benzene was removed under reduced pressure and the residue recrystallised from ether-hexane to afford **17** or **18**.

**17**, m.p. 110°; IR(KBr): 3300, 3030, 2970, 2910, 1645, 1585, 1100, 1010, 760, 750, 700  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ):  $\delta$ 1.30 (*t*, 3H,  $\text{C}-\text{CH}_3$ ), 3.56 (*s*, 3H,  $\text{N}-\text{CH}_3$ ), 4.15 (*q*, 2H,  $\text{O}-\text{CH}_2$ ), 6.74-8.45 (*m*, 10H, ArH and NH).

**18**, m.p. 121°; IR(KBr): 3220, 3020, 2950, 1590, 1520, 1055, 1000, 755, 740, 700  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ):  $\delta$ 1.33 (*t*, 3H,  $\text{C}-\text{CH}_3$ ), 3.46 (*s*, 3H,  $\text{N}-\text{CH}_3$ ), 4.14 (*q*, 2H,  $\text{OCH}_2$ ), 6.69-7.73 (*m*, 9H, ArH), 9.53 (*bs*, 1H, NH, exchangeable with  $\text{D}_2\text{O}$ ).

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## Synthesis of Substituted Indolo[3,2-*b*][1,4]benzodiazepin-5-ones & 1-Arylimidazo[4,5-*b*]indol-2(1*H*)-ones

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Ethyl 3-bromoindole-2-carboxylates (**2a-d**) on condensation with *p*-substituted anilines afford 3-(*p*-substituted anilino)indole-2-carboxylates (**3a-j**). Compounds **3a,b** on methylation give 3-(*N*-methyl-*p*-substituted anilino)indole-2-carboxylates (**4a,b**). These compounds (**4a,b**) have also been obtained by the condensation of **2a,b** with *p*-substituted *N*-methylanilines. Compounds **3c-j** and **4a,b** react with hydrazine hydrate to give the corresponding hydrazides (**5a-j**) which on treatment with NaNO<sub>2</sub> and AcOH furnish the respective azides (**6a-j**). The azides (**6a,b**) undergo thermal cyclization in diphenyl ether to give substituted indolo[3,2-*b*][1,4]benzodiazepin-5-ones (**7a,b**). However, the azides **6c-j** on cyclization yield 1-arylimidazo[4,5-*b*]indol-2(1*H*)-ones (**8c-j**).

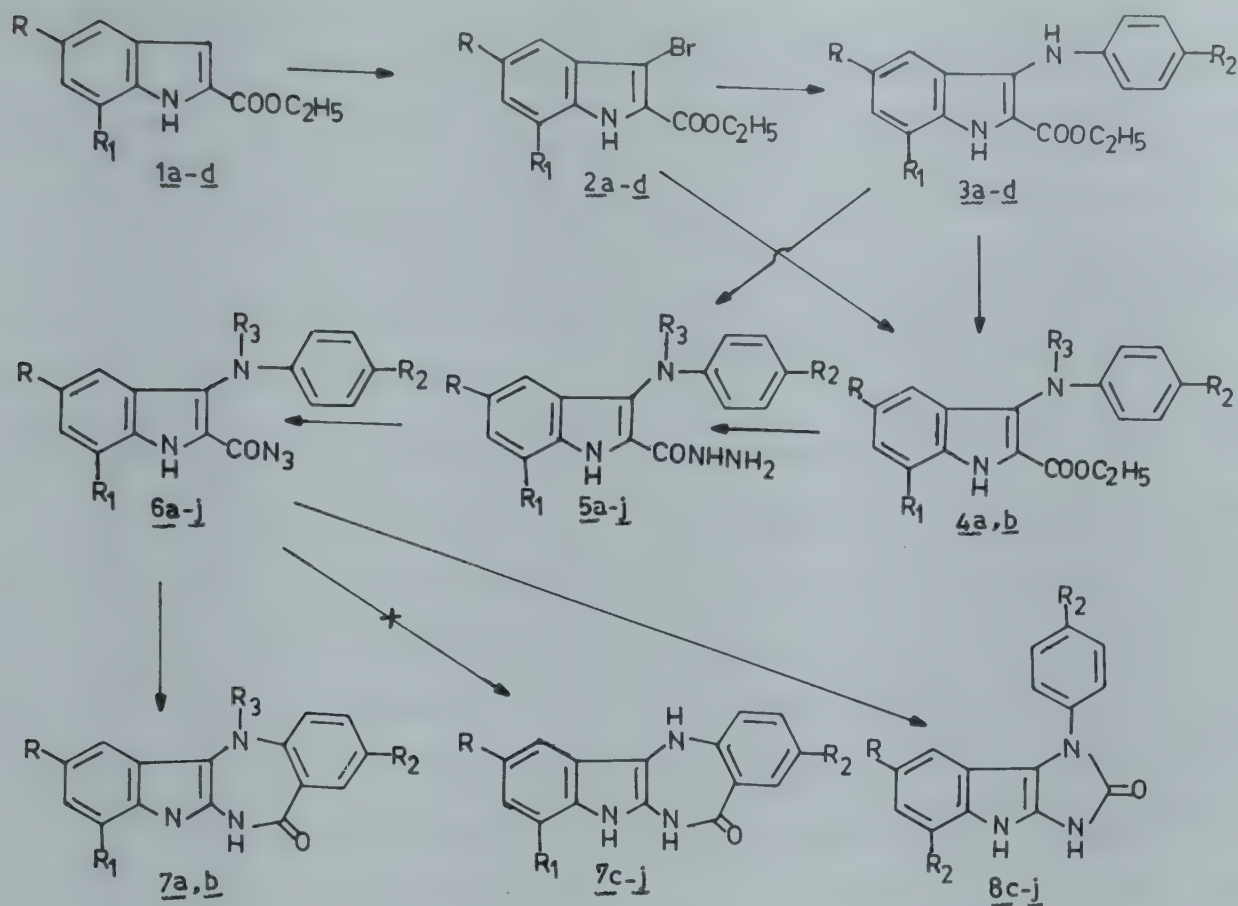
In continuation of our search<sup>1-6</sup> for pharmacologically potent indoles, several diazepinoindole derivatives have now been synthesised which may acquire a unique place in neuropharmacology<sup>7-12</sup>.

The required ethyl 3-bromoindole-2-carboxylates<sup>5</sup> (**2a-d**) were obtained by the bromination<sup>13</sup> of ethyl substituted indole-2-carboxylates (**1a-d**) and condensed with *p*-substituted anilines to get ethyl 3-(*p*-substituted anilino)indole-2-carboxylates (**3a-j**) (Scheme 1). Compounds **3a** and **3b** were subjected to methylation using dimethyl sulphate in alkali to get 3-(*N*-methyl-*p*-substituted-anilino)indole-2-carboxylates (**4a,b**). To confirm the methylation at phenyl NH in case of compound **3b**, **2b** was condensed with *N*-methyl-*p*-toluidine under similar experimental conditions to yield **4b**, identical (m.p., m.m.p; IR) with that obtained above. The esters **3c-j** and **4a,b** (Table 1) on refluxing with hydrazine hydrate (80%) in ethanol gave the required acid hydrazides which on treatment with nitrous acid at 0° furnished the required acid azides (**6a-j**; Table 1). The latter (**6a-j**) underwent thermal cyclization in diphenyl ether<sup>14</sup> in an inert atmosphere to give the desired substituted indolo[3,2-*b*][1,4]benzodiazepin-5-ones (**7a,b**). To our surprise, only 3-(*N*-methyl-*p*-substituted-anilino)indole-2-carboxyl azides (**6a,b**) gave the expected diazepinoindoles (**7a,b**), whereas azides **6c-j** produced the substituted imidazo[4,5-*b*]indol-2(1*H*)-ones (**8c-j**; Table 1). The structure of these compounds (**8c-j**) as imidazole derivatives was established on the basis of IR spectra and by analogy with literature reports<sup>15,16</sup>.

Ethyl 3-bromo-5-chloroindole-2-carboxylate (**2b**), obtained by bromination of **1b**, was condensed with *p*-toluidine in the presence of potassium carbonate, cupric oxide and pyridine to get ethyl

5-chloro-3-(*p*-methylanilino)indole-2-carboxylate (**3b**). The ester **3b** showed NH, NH and C=O absorption peaks at 3400, 3250 and 1705, respectively, in its IR† spectrum. The PMR† of **3b** exhibited a triplet and a quartet at 1.3 and 4.2 respectively due to ethyl moiety of the ester group. The sharp singlet at 8.9 was probably due to the proton of NH function bridged between indole and phenyl groups. The eight-proton multiplet which appeared at 6.6-7.3 was attributed to indole NH and aromatic protons<sup>17</sup>. The methyl protons of *p*-toluidine moiety appeared as a three-proton sharp singlet at 2.15. The compound **3b** on methylation gave ethyl 5-chloro-3-(*N*-methyl-*p*-substituted anilino)indole-2-carboxylate (**4b**). Methylation of this compound was confirmed on the basis of IR spectrum which was devoid of a peak due to NH function. The substituted esters (**4a,b**) and (**3c-j**) were condensed with hydrazine hydrate to get 3-(*p*-substituted-anilino)indole-2-carboxylic acid hydrazides (**5a-j**). The IR spectrum of **5a** displayed sharp peaks at 3350, 3250 and 1640 due to NH<sub>2</sub>, and NH and C=O groups, respectively. Compound **5d** showed the absence of a triplet and a quartet in comparison with its precursor in its PMR spectrum. The sharp and downfield signal at 10.8 accounted for the absorption of two protons, probably the NH<sub>2</sub> protons of the hydrazide moiety. A one-proton broad peak at 9.2 was assigned to the hydrazide NH proton. The multiplet which appeared in the aromatic region (6.6 - 7.2) integrated for nine protons, indicating that the other two NH protons resonated along with the aromatic protons.<sup>17</sup> The methyl protons of *p*-toluidine moiety

†IR  $\nu_{\max}$  in cm<sup>-1</sup> and PMR Chemical Shifts in  $\delta$ , ppm throughout the paper.



	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
a,	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	f,	Cl	Cl	CH <sub>3</sub>	H
b,	Cl	H	CH <sub>3</sub>	CH <sub>3</sub>	g,	CH <sub>3</sub>	H	Cl	H
c,	CH <sub>3</sub>	H	CH <sub>3</sub>	H	h,	Cl	H	Cl	H
d,	Cl	H	CH <sub>3</sub>	H	i,	Br	H	Cl	H
e,	Br	H	CH <sub>3</sub>	H	j,	Cl	Cl	Cl	H

Scheme 1

Table 1—Characterisation Data of Various Compounds Synthesised

Compd	Yield (%)	m.p. (°C)	Nature (solvent)	Mol. formula	Found (%) (Calc.)		
					C	H	N
3a	49	158	Light yellow needles (ethanol)	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	74.1 (74.0)	6.3 6.5	9.0 9.1
3b	56	154	Yellow needles (ethanol)	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> Cl	65.8 (65.8)	5.1 5.2	8.3 8.5
3e	50	165	Yellow needles (chloroform)	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> Br	57.7 (57.9)	4.6 4.6	7.2 7.5
3f	60	154	Colourless shining plates (chloroform)	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	59.6 (59.5)	4.3 4.4	7.5 7.7
3g	62	168	Colourless plates (benzene)	C <sub>18</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> Cl	65.6 (65.8)	5.0 5.2	8.3 8.5
3h	54	166	Yellow needles (chloroform)	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub>	58.5 (58.5)	4.0 4.0	8.0 8.0
3i	60	144	Yellow needles (chloroform)	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> BrCl	51.6 (51.8)	3.4 3.6	7.0 7.1

(Contd)

Table 1—Characterisation Data of Various Compounds Synthesised

Compd	Yield (%)	m.p. (°C)	Nature (solvent)	Mol. formula	Found (%) (Calc.)		
					C	H	N
3j	68	138	Light yellow needles (benzene)	$C_{17}H_{13}N_2O_2Cl_3$	53.0 (53.2)	3.2 3.4	7.1 7.3
4a	48	128	Colourless plates (benzene + pet. ether)	$C_{20}H_{22}N_2O_2$	74.5 (74.5)	6.8 6.8	8.7 8.7
4b	52	168	Brown needles (ethanol)	$C_{19}H_{19}N_2O_2Cl$	66.5 (66.6)	5.5 5.6	8.0 8.2
5a	60	212	Colourless shining plates (chloroform)	$C_{18}H_{20}N_4O$	70.0 (70.1)	6.5 6.5	18.0 18.2
5b	65	240	Yellow shining needles (ethanol)	$C_{17}H_{17}N_4OCl$	62.1 (62.1)	5.1 5.2	17.0 17.1
5c	62	242	Colourless needles (benzene)	$C_{17}H_{18}N_4O$	69.5 (69.4)	6.0 6.1	19.1 19.1
5d	60	268	Colourless shining plates (ethanol)	$C_{16}H_{15}N_4OCl$	61.3 (61.1)	4.7 4.8	17.6 17.8
5e	56	236	Light yellow needles (ethanol)	$C_{16}H_{15}N_4OBr$	53.3 (53.5)	4.0 4.2	15.5 15.6
5f	70	241	Light yellow granules (ethanol)	$C_{16}H_{16}N_4OCl_2$	55.2 (55.0)	4.0 4.0	15.9 16.0
5g	52	262(d)	Colourless needles (ethanol)	$C_{16}H_{15}N_4OCl$	61.3 (61.1)	4.7 4.8	17.7 17.8
5h	50	224	Yellow needles (ethanol)	$C_{15}H_{12}N_4OCl_2$	53.5 (53.7)	3.3 3.6	16.6 16.7
5i	60	286	Brown needles (ethanol)	$C_{15}H_{12}N_4OClBr$	47.4 (47.4)	3.1 3.2	14.7 14.8
5j	64	251	Yellow needles (ethanol)	$C_{15}H_{11}N_4OCl_3$	48.9 (48.7)	2.9 3.0	15.0 15.2
6a	80	102(d)	Light yellow powder	$C_{18}H_{17}N_5O$	—	—	—
6b	80	98(d)	Yellow powder	$C_{17}H_{14}N_5OCl$	—	—	—
6c	85	142(d)	Yellow amorphous powder	$C_{17}H_{15}N_5O$	—	—	—
6d	80	115(d)	Colourless amorphous powder	$C_{16}H_{12}N_5OCl$	—	—	—
6e	82	144(d)	Yellow amorphous powder	$C_{16}H_{12}N_5OBr$	—	—	—
6f	80	134(d)	Light yellow powder	$C_{16}H_{11}N_5OCl_2$	—	—	—
6g	66	124(d)	Yellow amorphous powder	$C_{16}H_{12}N_5OCl$	—	—	—
6h	68	152(d)	Brown powder	$C_{15}H_9N_5OCl_2$	—	—	—
6i	70	131(d)	Yellow amorphous powder	$C_{15}H_9N_5OBrCl$	—	—	—
6j	80	118(d)	Light yellow powder	$C_{15}H_8N_5OCl_3$	—	—	—
7a	60	348	Colourless granules (ethanol)	$C_{18}H_{17}N_3O$	74.3 (74.2)	5.8 5.8	14.3 14.4
7b	56	243	Reddish brown needles (pyridine)	$C_{17}H_{14}N_3OCl$	65.5 (65.5)	4.4 4.5	13.5 13.5
8c	60	328	Green needles (pyridine)	$C_{17}H_{15}N_3O$	73.5 (73.6)	5.3 5.4	15.0 15.2
8d	80	350	Pink granules (pyridine)	$C_{16}H_{12}N_3OCl$	64.7 (64.5)	4.0 4.0	14.1 14.1
8e	55	289	Reddish brown needles (ethanol)	$C_{16}H_{12}N_3OBr$	56.2 (56.1)	3.5 3.5	12.2 12.3
8f	60	224-26	Brown shining plates (chloroform + pet. ether)	$C_{16}H_{11}N_3OCl$	57.8 (57.8)	3.2 3.3	12.4 12.7
8g	40	168(d)	Brown needles (chloroform + pet. ether)	$C_{16}H_{12}N_3OCl$	64.5 (64.5)	4.0 4.1	14.0 14.1
8h	50	212	Yellow plates (benzene + pet. ether)	$C_{15}H_9N_3OCl_2$	56.5 (56.6)	2.7 2.8	13.0 13.2
8i	43	178(d)	Pink needles (benzene + pet. ether)	$C_{15}H_9N_3OBrCl$	49.4 (49.7)	2.2 2.5	11.5 11.6
8j	50	218(d)	Brown plates (benzene + pet. ether)	$C_{15}H_8N_3OCl_2$	51.0 (51.1)	2.1 2.3	11.7 11.9

appeared as a sharp singlet at 2.3. The hydrazides **5a-j** on treatment with  $\text{NaNO}_2/\text{AcOH}$  gave the corresponding azides (**6a-j**). The IR spectra of **6a-j** exhibited  $\text{N}_3$  absorption around 2160. 3-(*N*-methyl-*p*-substituted-anilino)-5-methylindole-2-carboxyazide (**6a**) when refluxed in diphenyl ether for 30 min in an inert atmosphere afforded 10-methylindolo[3,2-*b*][1,4]benzodiazepin-5-one (**7a**), the IR spectrum of which showed peaks at 1690 and 3110 due to  $\text{C}=\text{O}$  and  $\text{NH}/\text{NH}$  groups, respectively.

Following the above procedure compound **6b-j** were refluxed in diphenyl ether to get the respective diazepinoindoles. But, only compound **6b** gave the expected compound **7b** whereas compounds **6c-j** yielded the imidazol-2-ones (**8c-j**) instead of diazepinoindoles (**7c-j**). The IR spectra of **8c-j** exhibited a peak due to carbonyl group around 1740. This shifting of  $\text{C}=\text{O}$  absorption towards higher wave-number in comparison to the expected  $\text{C}=\text{O}$  absorption in diazepinoindolones (**7c-j**) led to the structure elucidation of new products. This was solved by comparing the physical and spectral data of **8c-j** with those of **7c-j**, which were prepared earlier<sup>6</sup> in our laboratory by an unambiguous method. The IR spectra were not superimposable and there was difference in the melting points. This reveals that the isocyanate obtained by Curtius rearrangement of the acid azide **6d** undergoes cyclization via nucleophilic attack of  $\text{NH}$  to yield 7-chloro-1-(*p*-methylphenyl)-imidazo[4,5-*b*]indol-2(1*H*)-one (**8d**). The IR spectrum of **8d** exhibited peaks at 3370, 3190 and 1745 due to  $\text{NH}$ ,  $\text{NH}$  and  $\text{C}=\text{O}$  groups respectively. The PMR spectrum of **8d** exhibited a sharp signal at 11.4 due to the proton of imidazole  $\text{NH}$ . The downfield shift was attributed due to the presence of adjacent carbonyl group. The eight-proton multiplet appearing in the aromatic region (6.8-7.5) was attributed to the indole  $\text{NH}$  and aromatic protons. The methyl protons were found to be merged with those of DMSO. These spectral data supported the assigned structure **8d**.

### Biological activity

Some of the compounds were screened for their antibacterial activity against *Esch. coli* and *Staph. aureus*. Among the 3-(*p*-substituted-anilino)indole-2-carboxylates (**3a-j**), only compound **3e** was highly active against *E. coli* whereas rest of the compounds were moderately active against *S. aureus*. Among the 1-(*p*-substituted-phenyl)imidazo[4,5-*b*]indol-2(1*H*)-ones (**8c-j**), compounds **8c** and **8j** exhibited weak activity against *S. aureus* whereas all other compounds showed moderate activity against *E. coli*. Compounds **5a-d** and **7a** showed moderate activity against both the organisms.

### Experimental Procedure

All the melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 297 IR spectrophotometer and PMR spectra in  $\text{DMSO}-d_6$  on a Varian XL-100 spectrophotometer using TMS as internal standard.

Ethyl 3-bromindole-2-carboxylates (**2a-d**) were prepared from ethyl indole-2-carboxylates (**1a-d**) as described in an earlier paper.<sup>5</sup>

#### Ethyl 3-(*p*-Substituted-anilino)indole-2-carboxylates (**3c-j**)

A mixture of **2** (0.005 mol), *p*-substituted aniline (0.005 mol), anhyd. potassium carbonate (0.7 g) and cupric oxide (0.025 g) in pyridine (5 ml) was heated under reflux for 14-16 hr, filtered and the residue washed with pyridine. The combined filtrate was poured onto ice cold dil. hydrochloric acid. The solid separated was filtered, washed with water, dried and purified by column chromatography over neutral alumina using appropriate eluant to give **3** (Table 1).

#### Ethyl 3-(*N*-methyl-*p*-substituted-anilino)indole-2-carboxylates (**4a,b**)

##### Method-1

A solution of **3a** or **3b** (0.0038 mol) in acetone (2.5 ml) was treated with a solution of potassium hydroxide (4.1 g) in water (20 ml) and dimethyl sulphate (3.6 ml) added to it dropwise. The reaction mixture was stirred for 30 min at room temperature, and the separated solid filtered, washed with water and crystallized from a suitable solvent to give **4a** or **4b** (Table 1).

##### Method-2

An equimolar mixture of **3a** or **3b** and substituted *N*-methylaniline (0.005 mol), anhydrous potassium carbonate (0.7 g), and cupric oxide (0.025 g) in pyridine (5 ml) was heated under reflux for 14-16 hr. The product **4a** or **4b** was obtained following a similar procedure as described for **3a-j**.

#### Substituted 3-(*N*-methyl-*p*-substituted-anilino)indole-2-carboxylic acid hydrazides (**5a,b**) and substituted 3-(*p*-Substituted-anilino)-indole-2-carboxylic acid hydrazides (**5c-j**)

An aqueous solution of hydrazine hydrate (5 ml, 80%) was added to a solution of **4a,b** or **3c-j** (0.0153 mol) in ethanol (10 ml). The reaction mixture was heated under reflux for 5 hr and cooled to room temperature. The hydrazide thus separated was filtered, washed with ethanol (2 ml), dried and crystallized from an appropriate solvent to give **5** (Table 1).

*Substituted 3-(N-methyl-p-substituted-anilino)indole-2-carbonyl azides (6a,b) and substituted 3-(p-substituted-anilino)indole-2-carbonyl azides (6c-j)*

To a suspension of **5** (0.0014 mol) in dioxane (1.5 ml), was added acetic acid (1.5 ml) dropwise at 0-2° and then sodium nitrite (0.35 g) in water (0.5 ml) with stirring at 0°. A pale yellow solid separated out immediately. The reaction mixture was stirred further for 30 min, filtered and washed successively with ice cold water (1 ml) and dioxane (1 ml). The precipitate (**6**; Table 1) was dried over phosphorus pentoxide *in vacuo* and used directly in the next step.

*Substituted indolo[3,2-b][1,4]benzodiazepin-5-ones (7a,b) and 1-arylimidazo[7,5-b]indol-2(1H)-ones (8c-j)*

A solution of **6** (0.08 mol) in diphenyl ether (10 ml) was added dropwise to hot diphenyl ether (10 ml) under nitrogen atmosphere. The temperature of the reaction mixture was maintained at 160-180° for 30 min. The solid that separated immediately was cooled, filtered, washed with pet. ether (60-80°), purified by column chromatography and crystallized from a suitable solvent to give **8** (Table 1).

#### Acknowledgement

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## Synthesis of 3-Aryl-1-tetralones

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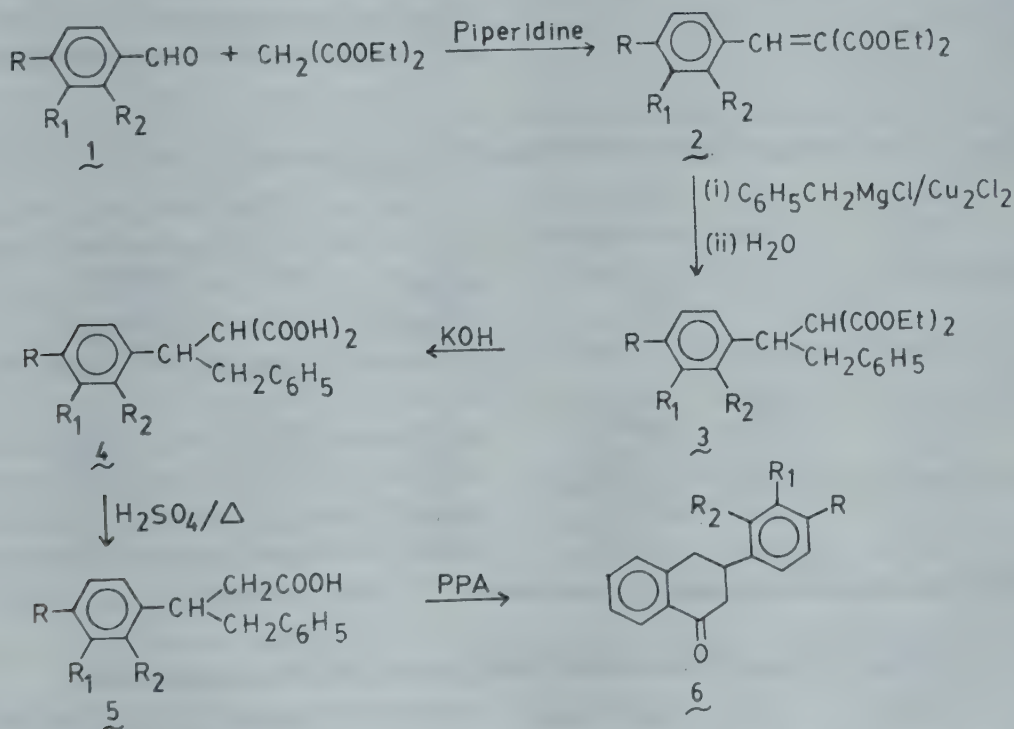
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A new method for the synthesis of 3-aryl-1-tetralones is presented. The tetralones synthesised have been characterised by elemental analysis and spectral data.

The title compounds, 3-aryl-1-tetralones are potential intermediates for the synthesis of differently substituted naphthalene compounds some of which are antimalarials<sup>1</sup>, and for higher membered aromatic ring systems. In view of the fact that only a few methods<sup>1-3</sup> are available for the synthesis of 3-aryl-1-tetralone ring system and with a view to building up polycyclic aromatic compounds, we have investigated a new and more general synthetic route (Scheme 1) to 3-aryl-1-tetralones.

In the compounds **2a-2f**, obtained in good yield (64-90%) by Knoevenagel condensation, each ester carbonyl is individually least reactive to direct addition since electron deficiency is greater at the  $\beta$ -position due to the combined effects of two carboxy groups. To further enhance conjugate addition, the reaction was carried out in the presence of catalytic amounts of copper(I) chloride. The conjugate adducts (**3a-3f**), obtained through usual methods, on saponification with aq. potassium hydroxide



1-6	R	R <sub>1</sub>	R <sub>2</sub>
a	H	H	H
b	CH <sub>3</sub>	H	H
c	OCH <sub>3</sub>	H	H
d	H	H	Cl
e	OCH <sub>3</sub>	OCH <sub>3</sub>	H
f	-O-CH <sub>2</sub> -O-		H (except 6)

SCHEME 1

gave 3-aryl-2-carboxy-4-phenylbutyric acids (**4a-4f**) (Table 1).

The above acids (**4a-4f**) on decarboxylation by heating with conc. sulphuric acid afforded 3-aryl-4-phenylbutyric acids (**5a-5f**) (Table 2).

All the butyric acids (**5a-5e**) except **5f** on cyclisation with PPA provided exclusively the desired 3-aryl-1-tetralones (**6a-6e**) (Table 3).

Interestingly, 3-(3,4-methylenedioxyphenyl)-4-phenylbutyric acid (**5f**) forms an exception. Unlike other butyric acids, cyclisation of **5f** with PPA gave 3-benzyl-(5,6-methylenedioxy)-1-indanone only, instead of the expected tetralone. This may be ascribed to the exceptionally strong activating influ-

ence of methylenedioxy group by increased mesomeric and electromeric effects inherited by the necessity of being planar with the benzene ring.

The structure of the ketones was established by IR and PMR spectra. The IR spectra of 3-aryl-1-tetralones (**6**) showed the carbonyl band at  $1680\text{ cm}^{-1}$  as expected. On the other hand, the indanone carbonyl stretching frequency appears at  $1700\text{ cm}^{-1}$ . The deshielding of  $C_8\text{-H}$  by the  $C=O$  group<sup>4</sup> in the PMR spectra of the tetralones established their structure as **6**. No such deshielding of *peri*-H has been noted in the case of the indanone as reported earlier<sup>4</sup>.

The present method, in addition to being simple and elegant, has the merit of placing the substituents in the required position in any of the phenyl ring.

### Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded in  $\text{CDCl}_3$  on a 90 MHz R32 Perkin-Elmer instrument using TMS as internal standard and IR spectra on a Perkin-Elmer IR-577 spectrophotometer.

### Diethyl benzalmalonates (**2**)

Diethyl benzalmalonate (**2a**<sup>5</sup>; yield 75%, b.p.  $163-64^\circ/5\text{ mm}$ ), diethyl *p*-methylbenzalmalonate (**2b**<sup>6</sup>;

Table 1—3-Aryl-2-carboxy-4-phenylbutyric Acids (**4a-4f**)

Compd	Yield (%)	m.p. °C	Mol. formula*
<b>4a</b>	53	68-69	$\text{C}_{17}\text{H}_{16}\text{O}_4$
<b>4b</b>	51	96-98	$\text{C}_{18}\text{H}_{18}\text{O}_4$
<b>4c</b>	63	162-63	$\text{C}_{18}\text{H}_{18}\text{O}_5$
<b>4d</b>	50	120-21	$\text{C}_{17}\text{H}_{15}\text{ClO}_4$
<b>4e</b>	59	147-48	$\text{C}_{19}\text{H}_{20}\text{O}_6$
<b>4f</b>	65	160-61	$\text{C}_{18}\text{H}_{16}\text{O}_6$

\*Satisfactory elemental analyses were obtained for all the compounds.

Table 2—Characterisation and PMR Data of 3-Aryl-4-phenylbutyric Acids (**5a-5f**)

Compd	Yield (%)	m.p. (lit., m.p.) °C	Mol. formula*	PMR ( $\text{CDCl}_3$ ), $\delta_{\text{ppm}}$			
				O    C-OH	Ar-H	Aliphatic-H ( $C_2$ , $C_3$ - and $C_4$ -H)	Others
<b>5a</b>	79	92-93 (92-93) <sup>2</sup>	—	12.0	7.0-7.4	2.7-3.55	—
<b>5b</b>	86	155-56	$\text{C}_{17}\text{H}_{18}\text{O}_2$	11.5	6.9-7.4	2.7-3.5	2.1
<b>5c</b>	75	120-21	$\text{C}_{17}\text{H}_{18}\text{O}_3$	11.5	6.7-7.3	2.8-3.4	3.8
<b>5d</b>	80	60-61	$\text{C}_{16}\text{H}_{15}\text{ClO}_2$	12.0	7.1-7.3	2.7-3.4	—
<b>5e</b>	71	115-17	$\text{C}_{18}\text{H}_{20}\text{O}_4$	11.0	6.6-7.3	2.8-3.5	3.8
<b>5f</b>	63	145-48	$\text{C}_{17}\text{H}_{16}\text{O}_4$	11.5	6.4-7.3	2.8-3.55	5.85

\*Satisfactory elemental analyses were obtained for all the compounds.

Table 3—Characterisation and PMR Data of 3-Aryl-1-tetralones (**6**)

Compd	Yield (%)	m.p. (lit., m.p.) °C	Mol. formula*	PMR ( $\text{CDCl}_3$ ), $\delta_{\text{ppm}}$			
				$C_8\text{-H}$	Ar-H	Alicyclic-H ( $C_2$ , $C_3$ - and $C_4$ -H)	Others
<b>6a</b>	75	64-65 (65-66) <sup>2</sup>	—	7.9-8.15	7.0-7.7	2.6-3.6	—
<b>6b</b>	76	69-70	$\text{C}_{17}\text{H}_{16}\text{O}$	7.9-8.15	7.0-7.7	2.6-3.6	2.2
<b>6c</b>	60	105-6	$\text{C}_{17}\text{H}_{16}\text{O}_2$	7.95-8.2	6.7-7.6	2.6-3.7	3.8
<b>6d</b>	64	64-65	$\text{C}_{16}\text{H}_{13}\text{ClO}$	7.9-8.1	7.0-7.7	2.6-3.7	—
<b>6e</b>	55	118-19	$\text{C}_{18}\text{H}_{18}\text{O}_3$	8.0-8.2	6.6-7.6	2.9-3.3	3.8

\*Satisfactory elemental analyses were obtained for all the new compounds.

yield 64%, m.p. 44-45°), diethyl *p*-methoxybenzalmalonate (**2c**<sup>7</sup>; yield 90%, b.p. 190-91°/4 mm), diethyl *o*-chlorobenzalmalonate (**2d**<sup>8</sup>; yield 65%, b.p. 182-85°/5 mm), diethyl 3,4-dimethoxybenzalmalonate (**2e**; yield 80%, b.p. 190-92°/5 mm), and diethyl 3,4-methylenedioxybenzalmalonate (**2f**; yield 88%, b.p. 220-22°/5 mm) were prepared according to the method of Allen and Spangler<sup>5</sup>. Satisfactory microanalyses were obtained for all the new compounds.

### 3-Aryl-2-carboxy-4-phenylbutyric acids (**4**): Typical procedure

To a solution of benzylmagnesium chloride, prepared from magnesium turnings (12 g) and benzyl chloride (64 g) in dry ether (300 ml), was added analar cuprous chloride (3 g) in small portions with stirring when a vigorous reaction occurred and changed the colour of the solution to intense green. After stirring for 30 min at room temperature, the reaction flask was surrounded with ice, and the reaction mixture treated dropwise with a solution of diethyl benzalmalonate (62 g) in ether (120 ml). The stirring was continued further for 3 hr and the mixture left overnight. The Grignard complex was decomposed with water. The organic layer was decanted, washed with 2 *N* hydrochloric acid, then with water, dried and evaporated. The residue, ethyl 2-carbethoxy-3,4-diphenylbutyrate was as such subjected to hydrolysis as given below:

A warm solution of ethyl 2-carbethoxy-3,4-diphenylbutyrate (50 g) was added dropwise to a stirred solution of potassium hydroxide (35 g) in water (40 ml) when the solution started refluxing owing to the heat of saponification. After the completion of addition, the solution was refluxed with stirring for 3 hr. The reaction mixture was diluted with water (60 ml), cooled in an ice-bath and neutralised with dil. hydrochloric acid. An oily layer separated out which soon solidified. It was filtered, washed with water and recrystallised from methyl alcohol to give 2-carboxy-3,4-diphenylbutyric acid (**4a**; 37.5 g).

### 3-Aryl-4-phenylbutyric acids (**5**): Typical procedure

To melted 2-carboxy-3,4-diphenylbutyric acid (**4a**; 30 g), a solution of conc. sulphuric acid (60 g) in

water (80 ml) was added dropwise with stirring. After the addition of sulphuric acid was complete, the reaction mixture was refluxed for 8 hr and cooled. The resultant 3,4-diphenylbutyric acid was filtered, dissolved in sodium bicarbonate solution and the solution boiled with norite for 30 min. The hot solution was filtered, cooled and neutralised with dil. hydrochloric acid. The solid that separated was filtered, dried and crystallised from benzene to give 3,4-diphenylbutyric acid (**5a**; 20 g).

### 3-Aryl-1-tetralones (**6**): Typical procedure

Polyphosphoric acid (40 g), previously warmed to 90° was added in one lot with manual stirring to molten **5a** (12 g) and the stirring continued for 30 min. An additional quantity of polyphosphoric acid (40 g) was then added and the mixture heated on a water-bath for 30 min with stirring and left overnight. The cold mixture was hydrolysed by adding ice (100 g) and cold water (20 ml). When the hydrolysis was complete as indicated by the disappearance of orange viscous material and the appearance of a yellow oil, the mixture was transferred to a separating funnel and extracted with ether (3 × 50 ml). The combined ether extracts were washed successively with water, sodium hydroxide solution (2 × 60 ml), aq. acetic acid (60 ml), sodium bicarbonate solution (60 ml) and finally with water. The ether solution was dried and solvent removed to give 3-phenyl-1-tetralone (**6a**; 8.3 g).

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## COSY & Hetero-COSY 2D NMR Measurements on 1,4-Diphenyl-1-azabutadiene: Carbon-13 NMR Chemical Shift Assignments

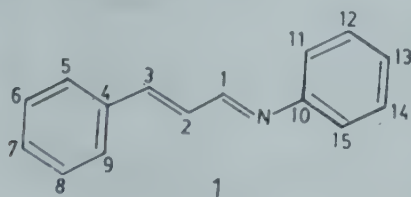
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Complete  $^{13}\text{C}$ -NMR chemical shift assignments in 1,4-diphenyl-1-azabutadiene (**1**) have been made with the help of 2D  $^{13}\text{C}/^1\text{H}$ -heteronuclear shift correlation and  $^1\text{H}$ -homonuclear shift correlation NMR spectroscopy.

In recent years, the development of two-dimensional NMR spectroscopy<sup>1-5</sup> has tremendously increased the potential of NMR technique in solving intricate structural and stereochemical problems in organic chemistry. The available modes of spreading the spectrum in two dimensions require plotting the same or different NMR parameters along two axis, thus enabling correlation between homo-<sup>1,7</sup> and hetero-nuclear chemical shifts<sup>8,9</sup>, or between homo- or hetero-nuclear coupling constants (long and short range) and chemical shifts. Instances of application of this method are multiplying at a fast pace<sup>9-17</sup>. We report herein application of  $^{13}\text{C}/^1\text{H}$  heteronuclear shift correlation and  $^1\text{H}$ -homonuclear shift correlation 2D NMR measurements for complete  $^{13}\text{C}$ -chemical shift assignments in 1,4-diphenyl-1-azabutadiene (**1**). Literature records determination of some of  $^1\text{H}$  chemical shifts in **1** using INDOR NMR spectral technique<sup>18</sup>, albeit, no attempt appears to have been made towards assignment of  $^{13}\text{C}$  chemical shifts.



### Materials and Methods

1,4-Diphenyl-1-azabutadiene (**1**) was prepared according to literature method<sup>19</sup>.  $^1\text{H}$  and  $^{13}\text{C}$  NMR (both 1D and 2D) were recorded on a BRUKER 270 MHz instrument. Homonuclear  $^1\text{H}$ -shift correlation 2D NMR spectrum<sup>1,7</sup> was recorded using the pulse sequence D1-90-DO-45-FID with chemical shifts and coupling constants along both  $F_2$  and  $F_1$  dimensions. D1 is the relaxation delay time (1.0 ms) and DO is the incremented delay time (with increments of 1.0 ms). Total of 512 spectra were recorded (8 scans each). Digital reso-

lution was about 2.1 Hz/point. The  $^{13}\text{C}/^1\text{H}$  shift correlation spectrum was recorded using polarization transfer from  $^1\text{H}$  to  $^{13}\text{C}$  via  $J_{\text{C-H}}$ . The pulse sequence used was

$$^1\text{H} = \text{D0} - 90 - \text{D0} - \text{D0} - \text{D3} - 90$$

$$^{13}\text{C} = \text{D1} - 180 - 90 - \text{D4} - \text{FID}$$

where D0, D1 are  $^1\text{H}$  relaxation delay times (1.0 s). D3 is wait for optimum polarization transfer (3.5 ms) and D4 is wait for antiphase  $^{13}\text{C}$  nuclei to rephase (1.75 ms). D0 is incremented delay time (evolution time) with increments of 1.111 ms. Spectral width in  $F_2$  dimension was 3731.60 Hz and in  $F_1$  dimension 379.81 Hz. Total of 256 spectra were accumulated (64 scans each). Resolution was 14.59 Hz/point along  $F_2$  dimension and 1.48 Hz/point along  $F_1$  dimension.

### Results and Discussion

A priori, the proton-decoupled  $^{13}\text{C}$  NMR spectrum of **1** presents quite a complex scenario hav-

Table 1—Carbon-13 Chemical Shift Assignments and Corresponding  $^1\text{H}$  Chemical Shift Values in **1** as revealed in Its 2D-Hetero COSY and COSY Spectra

Carbon	Chemical Shift ( $\delta$ , ppm)	
	$^{13}\text{C}$	$^1\text{H}$
C-1	161.47	8.26
C-2	128.56	7.14
C-3	143.86	7.11
C-4	135.53	—
C-5/9	127.40	7.53
C-6'/8	128.80*	7.37
C-7	129.47	7.35
C-10	151.69	—
C-11'/15	120.80	7.20
C-12/14	129.07*	7.38
C-13	126.00	7.23

\*Temperature assignment

ing several closely-spaced signals (Table 1) with no direct or reliable means of distinguishing between them.

However, based on SFORD, the two quaternary carbon signals (C-4, C-10)<sup>†</sup> could initially be located at  $\delta$  135.53 and 151.69 respectively. The majority of remaining  $^{13}\text{C}$  chemical shifts in **1** were determined from C-H and H-H connectivities revealed in its 2D hetero-COSY- and COSY spectra shown in Figs 1 and 2 respectively.

The lowest field signal in the  $^{13}\text{C}$  NMR spectrum of **1** ( $\delta$  161.47) which correlated with the

lowest field resonance in the  $^1\text{H}$  NMR spectrum ( $\delta$  8.26) is ascribed to  $\text{C}_1\text{-H}$ . Two other signals located at  $\delta$  143.86 (*d* in SFORD) and 128.56 displaying correlations, respectively, with proton resonance at  $\delta$  7.11 and 7.14 (Fig. 1) could be assigned to the olefinic carbons, C-3 and C-2, respectively; the relative positions of  $\text{C}_2\text{-H}$  and  $\text{C}_3\text{-H}$  signals became apparent from (a) the observation of substantial coupling of  $\text{C}_2\text{-H}$  resonance ( $\delta$  7.14) with the  $\text{C}_1\text{-H}$  signal ( $\delta$  8.26) (Fig. 2) and (b) homo-spin decoupling experiments involving irradiation of  $\text{C}_1\text{-H}$  signal ( $\delta$  8.26) indi-

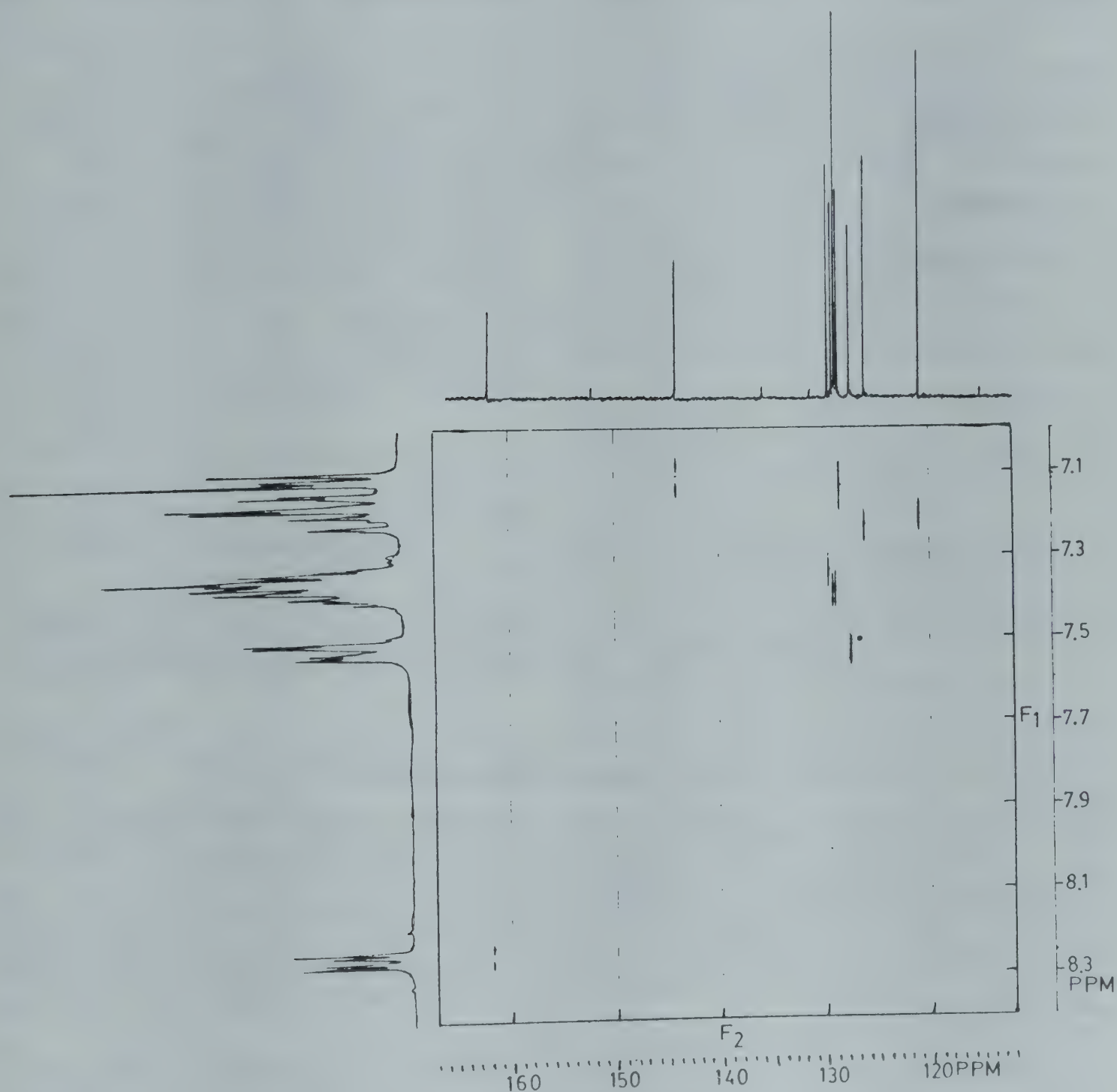
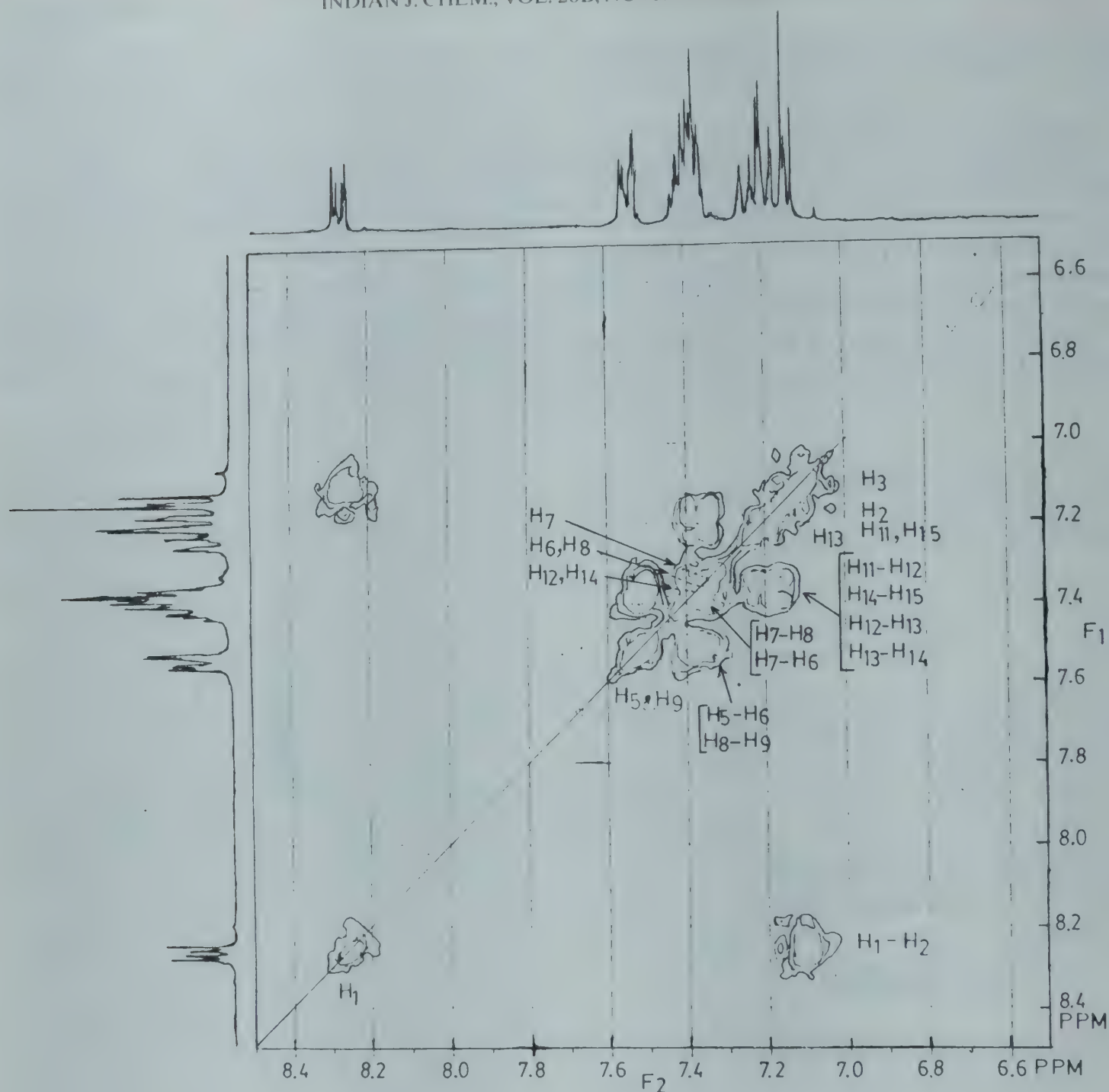


Fig. 1— $^{13}\text{C}/^1\text{H}$  hetero-COSY spectrum of **1**

<sup>†</sup>Arbitrary numbering pattern in **1** has been adopted for convenience of description of spectral results.

Fig. 2—270 MHz  $^1\text{H}$  COSY spectrum of **1**

cating proximate location of  $\text{C}_2\text{—H}$  and  $\text{C}_3\text{—H}$ . Again, the signal at  $\delta$  127.4 correlated with a 2H multiplet at  $\delta$  7.53 which protons, in turn, displayed coupling with aromatic protons in the multiplet around  $\delta$  7.37 (Fig. 2); the 2H multiplet at  $\delta$  7.53 was thus attributed to *ortho* hydrogens ( $\text{C}_5\text{—H}$ ,  $\text{C}_9\text{—H}$ ) and the  $^{13}\text{C}$  signal at  $\delta$  127.4 to *ortho* carbons ( $\text{C—5}$  and  $\text{C—9}$ ).

The  $^{13}\text{C}$  NMR reveals two more resonances, located upfield with respect to the rest, at  $\delta$  120.8 and 126.0. These were observed (in the hetero-COSY spectrum; Fig. 1) to correlate with protons

in the upfield multiplet (in the  $^1\text{H}$  NMR spectrum) at  $\delta$  7.20 and 7.23 respectively. In consonance with earlier observations<sup>20–23</sup> on the relative upfield shift of resonance due to *ortho* and *para* carbons and hydrogens with respect to *meta* nuclei in the N-phenyl ring in benzylideneaniline, N,N-dimethylaniline etc.<sup>\*\*</sup>, the signals at  $\delta$  120.8 and

<sup>\*\*</sup>The presently-observed upfield shift of *o*- and *p*- carbons ( $\delta$  120.8 and  $\delta$  126.0) with respect to *meta* carbons may have its origin in the mesomeric release from the nitrogen atom into the 1-phenyl ring, which, in turn, requires the 1-phenyl group to attain an orientation orthogonal to the  $\text{C}=\text{C}\text{—C}=\text{N}$  plane. Such an orientation for **1** has also been suggested from the  $^1\text{H}$  NOE and solvent-induced shifts measurements by Anteunis *et al.*<sup>18</sup>.

Anteunis *et al.*<sup>18</sup> report  $\delta$  values 7.00 and 7.02 for  $\text{C}_3\text{—H}$  and  $\text{C}_2\text{—H}$ , respectively, in  $\text{CCl}_4$  solvent, based on INDOR studies on **1**

126.0 in **1** were ascribed to *ortho* carbons (C-11, C-5) and *para* carbon (C-13) respectively.

Of the three signals at  $\delta$  128.8, 129.07 and 129.47, the one at 128.8 is revealed to be due to *meta* carbons (C<sub>6</sub> and C<sub>8</sub>), based on their observed correlation with proton resonances at  $\delta$  7.37 (Fig. 1) and observations of *ortho* couplings (Fig. 2) between protons at  $\delta$  7.37 (C<sub>6</sub>-H, C<sub>8</sub>-H) and  $\delta$  7.53 (C<sub>5</sub>-H, C<sub>9</sub>-H).

The candidates for remaining signals at  $\delta$  129.07 and 129.47 are the *meta* carbons (C-12, C-14) and *para* carbon (C-7). The distinction between these appears possible on the basis of (i) the COSY spectrum (Fig. 2), which reveals a correlation between proton resonances at  $\delta$  7.20 and 7.23 (which have now been assigned to *ortho* and *para* hydrogens of the N-phenyl ring) and the signal at 7.38 (*meta* hydrogens), and (ii) the hetero-COSY spectrum (Fig. 1) which suggests connectivity of the latter signal ( $\delta$  7.38) with the carbon resonance at  $\delta$  129.07. The signal at  $\delta$  129.47 is thus due to the *para* carbon (C-7) C<sub>7</sub>; the latter assignment is also in accord with the observed correlation of the (attached) proton resonance at  $\delta$  7.35 (*para*-hydrogen) with the signal around  $\delta$  7.37 (assigned to *meta* hydrogens, C<sub>6</sub>-H, C<sub>8</sub>-H) in the COSY spectrum.

It is of interest to mention here that the presently-derived chemical shifts of C-2 and C-3 ( $\delta$  128.56 and 143.86 respectively) in **1** are suggestive of substituent chemical shift effects of the order of +15.36 and +6.90, for the group CH=N-Ph, on  $\alpha$  and  $\beta$  carbons, respectively, of trans-disubstituted olefinic bond. Calculations based on reported <sup>13</sup>C chemical shift assignments in styrenes<sup>2,4</sup>.

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## Studies in Nucleosides: Part XIX – Synthesis of 4,6-Disubstituted Derivatives of 1- $\alpha$ -D-Arabinofuranosylpyrazolo[3,4-*d*]pyrimidines & Their Antiviral Activity†

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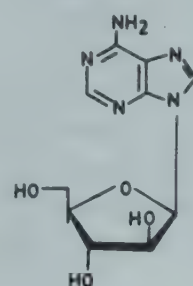
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4-Amino-6-methylthio-1- $\alpha$ -D-Arabinofuranosyl derivatives of pyrazolo[3,4-*d*]pyrimidine (**9**), 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine (**10**), 4-amino-6-methoxypyrazolo[3,4-*d*]pyrimidine (**14**), 4-methoxy-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**15**) and 6-amino-4-methoxypyrazolo[3,4-*d*]pyrimidine (**17**) have been synthesised. Of the compounds **9**, **10**, **12**, **14**, **15** and **17** screened against Ranikhet disease virus and vaccinia virus, only **12** and **17** show 70 and 50% inhibition respectively of RDV virus. The remaining compounds exhibit either weak activity or are found inactive.

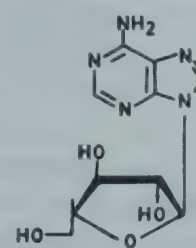
9- $\beta$ -D-Arabinofuranosyladenine (Ara-A) (**1**) is a potent antiviral agent and is active against several DNA viruses<sup>1,2</sup>. More recently its unnatural  $\alpha$ -isomer, 9- $\alpha$ -D-arabinofuranosyladenine (**2**) is found to be a substrate for adenosine kinase and it inhibits the growth of both RNA and DNA viruses<sup>3</sup>. Further the  $\alpha$ -anomer (**3** of 8-azaadenine arabinoside is also found effective against both DNA and RNA viruses<sup>4</sup>. Viral multiplication is known to be inhibited by several 4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines. The compounds that effectively inhibit the viral multiplication contain methylmercapto group in pyrazolo-pyrimidine moiety and further the nucleoside such as **4** is found more active than the corresponding heterocyclic base<sup>5</sup>. These reports prompted us to undertake the synthesis of 4,6-disubstituted-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidines. In the present paper we report the synthesis of 1- $\alpha$ -D-arabinofuranosyl-4-amino-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**9**), 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine (**10**), 4-amino-6-methoxypyrazolo[3,4-*d*]pyrimidine (**14**), 4-methoxy-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**15**) and 6-amino-4-methoxypyrazolo[3,4-*d*]pyrimidine (**17**).

Condensation of chloromercuric complex (**5**) of 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine<sup>6</sup> with 2,3,5-tri-O-benzoyl-D-arabinofuranosyl bromide (**6**)<sup>7</sup> in anhyd. toluene at 120° led to a mixture of 4,6-dimethylthio-1-(2,3,5-tri-O-benzoyl- $\alpha$ -D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**8**) (yield 30%) and 4,6-dimethylthio-1-(2,3,5-tri-O-benzoyl- $\beta$ -D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**) (yield 2.5%).



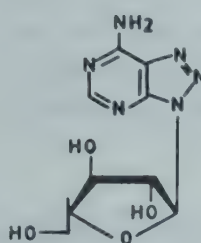
**9- $\beta$ -isomer**

**1**, Antiviral  
(against DNA virus)



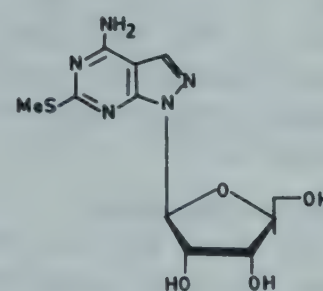
**9- $\alpha$ -isomer**

**2**, Antiviral  
(against both DNA & RNA viruses)



**9- $\alpha$ -isomer**

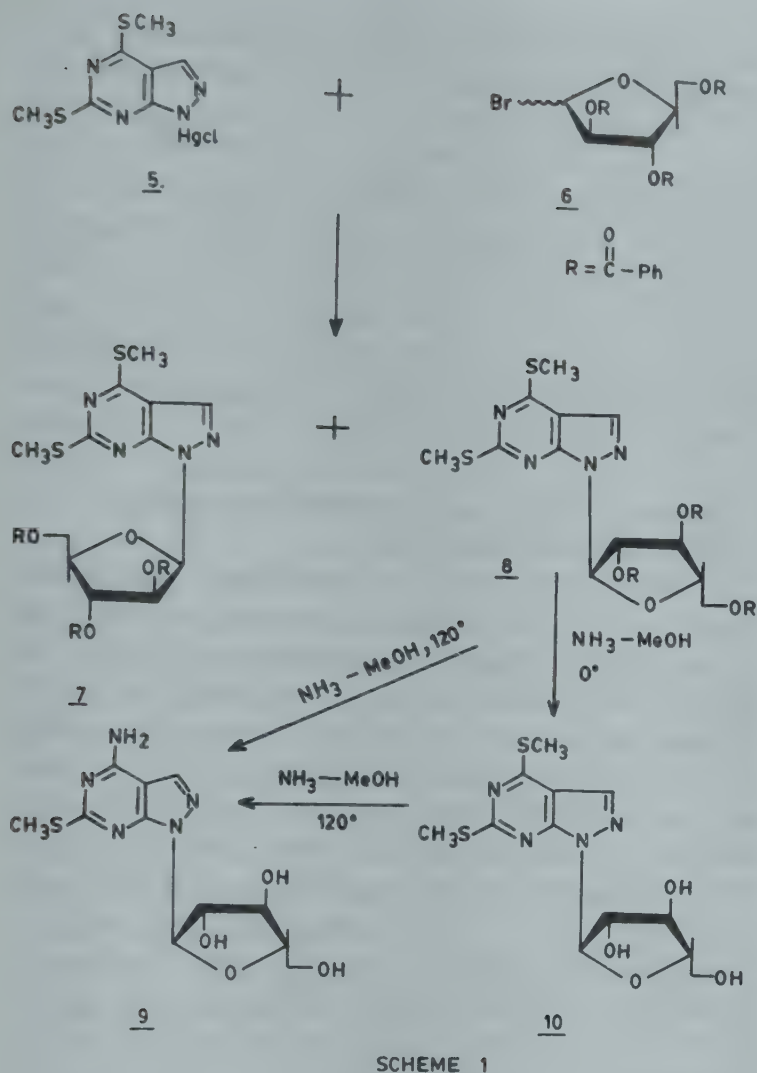
**3**, Antiviral  
(against both DNA & RNA viruses)



**4**  
Antiviral  
(against HSV)

These were separated by preparative TLC over SiO<sub>2</sub> plates. The UV data of **7** and **8** were suggestive of the attachment of arabinose moiety at N-1 in the heterocyclic base. The  $\alpha$ - and  $\beta$ -configurations of **8** and **7** respectively were supported by their PMR data (see Experimental). The chemical shifts and coupling constants (*J*) of anomeric protons (H-1') in **8** and **7** were in accord with the reported values for  $\alpha$ - and  $\beta$ -arabinosides<sup>8-10</sup>. The *J*-value of the anomeric proton in protected arabinosides, in general, was found lower than that of the corresponding de-

† CDRI Communication No. 3998.

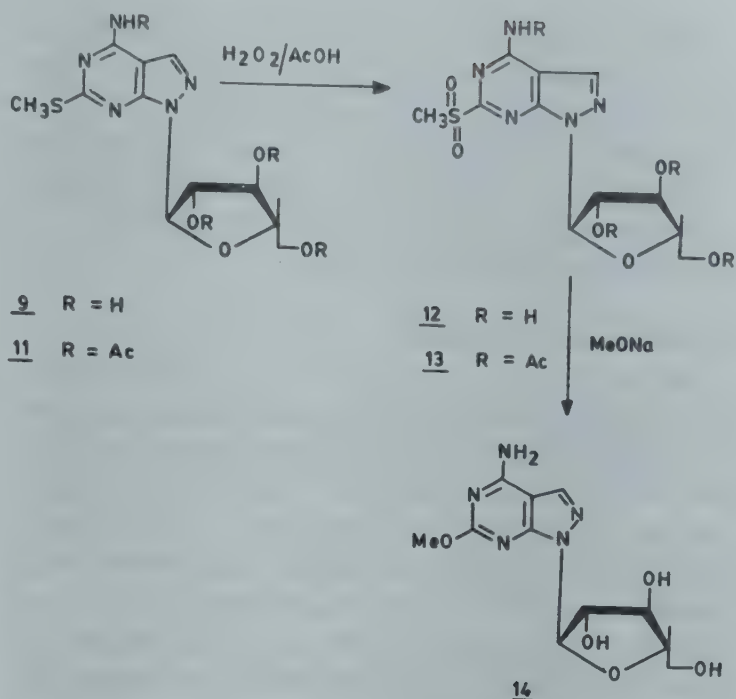


SCHEME 1

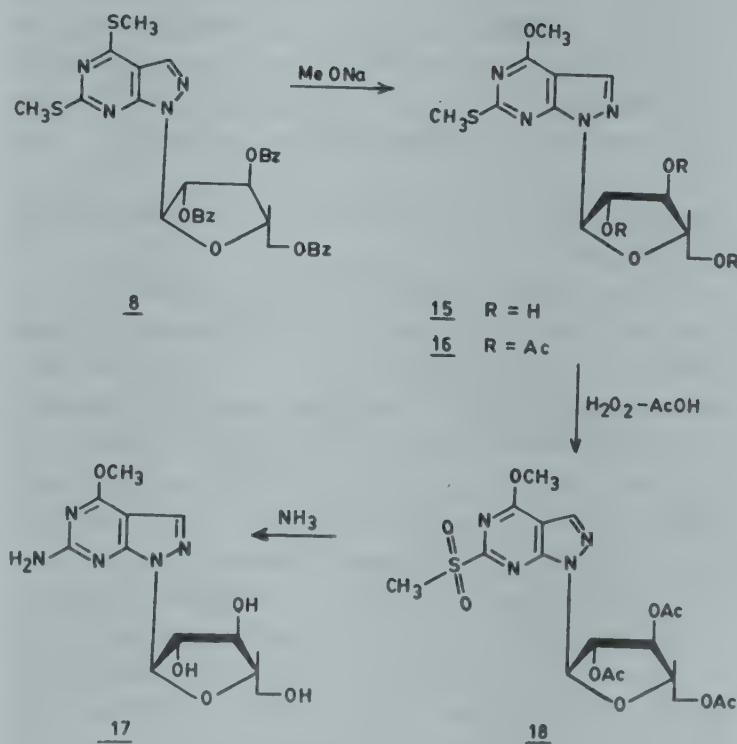
blocked arabinosides, in conformity with the literature observations<sup>11</sup>.

Treatment of **8** with methanolic ammonia at ambient temperature afforded 4,6-dimethylthio-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**10**) in 43% yield. In the protected arabinoside (**10**) there are two thiomethyl functions at 4- and 6-positions of the heterocyclic moiety. Substituent at position-4 is relatively more reactive than that at position-6 in nucleophilic substitution reactions<sup>12</sup>. This was found to be so for **10** also, which when heated with ethanolic ammonia in a steel bomb at  $128^\circ$ , afforded 4-amino-6-methylthio-1- $\alpha$ -D-arabinoside (**9**) in excellent yield (90%). The blocked arabinoside on similar treatment gave **9** in poor yield (38%).

Acetylation of **9** (Scheme 2) with,  $\text{Ac}_2\text{O}$  and pyridine gave the tetraacetylated derivative (**11**) in 80% yield. Oxidation of **11** with  $\text{KMnO}_4$  in acetic acid at  $0^\circ$  furnished 4-acetamido-6-methylsulphonyl-1-(2,3,5-tri-O-acetyl- $\alpha$ -D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**13**) in good yield (75%). Treatment of **13** with MeONa in absolute methanol gave 4-amino-6-methoxy-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**14**) in 75% yield.



SCHEME 2



SCHEME 3

Deblocking of the arabinoside (**8**) (Scheme 3) with sodium methoxide in absolute methanol at ambient temperature yielded the corresponding deblocked arabinoside, 4,6-dimethylthio-1- $\alpha$ -D-arabinofuranosyl[3,4-*d*]pyrimidine (**10**) (yield 30%) and 4-methoxy-6-dimethylthio-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**15**) in 40% yield. Here again the methylthio substituent at position-4 in **10** was selectively replaced by an oxygen function. The mixture of **10** and **15** was separated on  $\text{SiO}_2$  column. Acetylation of **15** with  $\text{Ac}_2\text{O}$  and pyridine furnished the acetylated derivative (**16**) in 80% yield, which on oxidation with

KMnO<sub>4</sub> in acetic acid at 0° afforded 4-methoxy-6-methylsulphonyl-1- $\alpha$ -D-(2,3,5-tri-O-acetyl arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**18**) in very good yield (80%). Compound **18** on treatment with liquid NH<sub>3</sub> at 90° finally gave 6-amino-4-methoxy-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**17**) in 75% yield.

### Experimental Procedure

Melting points were taken in a silicon oil-bath and are uncorrected. UV spectra were recorded on a Perkin Elmer-202 spectrophotometer ( $\lambda$  in nm), IR spectra on a Perkin-Elmer-157 grating infracord ( $\nu_{\max}$  cm<sup>-1</sup>) and PMR on a Perkin-Elmer-360 mL at 60 MHz (chemical shift values in  $\delta$  scale) using TMS as internal reference. The homogeneity of compounds was routinely checked on silica gel-GF-254 plates and the spots were located under a mineralite UV lamp/by iodine vapours/by spraying either with 10% sulphuric acid solution in ethanol or with 2% *p*-anisaldehyde in 10% sulphuric acid solution in ethanol followed by heating at 100° for 30 min. The solvents were evaporated under reduced pressure below 30°.

#### Arabinosylation of 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine

To an azeotropically dried suspension of chloromercuri complex (**5**) of 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine (5 g, 11.2 mmol) in anhyd toluene (100 ml) was added slowly, 1-bromo-2,3,5-tri-O-benzoyl-D-arabinose (9 g, 17.9 mmol) in anhyd. toluene (50 ml) at 60°. The mixture was refluxed for 4 hr and filtered while hot. The solvent from the filtrate was removed under reduced pressure, the residue triturated with anhyd. hexane, extracted with chloroform, washed with aq KI (3  $\times$  50 ml, 30%), water (3  $\times$  50 ml), dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed. The crude product (5 g) obtained, was purified by preparative TLC chromatography on silica gel plates (solvent: CHCl<sub>3</sub>–MeOH, 95.5: 0.5 v/v) to give the blocked nucleosides (**8**) and (**7**).

#### 4,6-Dimethylthio-1- $\alpha$ -(2,3,5-tri-O-benzoyl-D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**8**)

It was obtained as a colourless foam, yield (4.6 g, 30%); UV (MeOH): 238, 273; IR (KBr): 1740 (C=O); MS: 657 (M<sup>+</sup> + 1); PMR (CDCl<sub>3</sub>): 8.09 (s, 1H, H-3), 8.00-7.70 (*m*, 6H, ArH), 7.49-7.15 (*m*, 9H, Ar–H), 6.20 (*d*, 1H, *J* = 2 Hz, H-1'), 5.8-5.5 (*m*, 1H, H-2'), 5.0-4.7 (*m*, 2H, H-3' & H-4'), 4.65-4.40 (*m*, 2H, H-5'), 2.51 (*s*, 6H, 2  $\times$  SCH<sub>3</sub>) (Found: C, 60.5; H, 4.6; N, 8.8. C<sub>33</sub>H<sub>28</sub>N<sub>4</sub>O<sub>7</sub>S<sub>2</sub> requires C, 60.4; H, 4.3; N, 8.5%).

#### 4,6-Dimethylthio-1- $\beta$ -(2,3,5-tri-O-benzoyl-D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**7**)

It was also obtained as a colourless foam, yield (0.36 g, 2.3%); UV(MeOH): 232, 268; IR (KBr): 1740 (C=O); PMR (CDCl<sub>3</sub>): 8.15 (*s*, 1H, H-3), 8.10-7.85 (*m*, 6H, ArH), 7.50-7.25 (*m*, 9H, ArH), 6.35 (*d*, 1H, *J* = 6.0 Hz, H-1'), 5.80 (*m*, 1H, H-2'), 5.20 (*m*, 1H, H-3'), 4.81-4.62 (*m*, 3H, 5'-CH<sub>2</sub> and H-4'), 2.55 (*s*, 3H, SCH<sub>3</sub>) and 2.54 (*s*, 3H, SCH<sub>3</sub>) (Found: C, 60.6; H, 4.5; N, 8.2. C<sub>33</sub>H<sub>28</sub>N<sub>4</sub>O<sub>7</sub>S<sub>2</sub> requires C, 60.4; H, 4.3; N, 8.5%).

#### 4,6-Dimethylthio-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**10**)

A mixture of **8** (4 g, 6 mmol) and methanolic ammonia (150 ml MeOH, saturated with NH<sub>3</sub> at 0°) was kept at ambient temperature for 24 hr. MeOH and excess of NH<sub>3</sub> were removed under reduced pressure, the residue dissolved in water (100 ml) and extracted with ether (4  $\times$  10 ml). Water was removed from aqueous extract *in vacuo* and the product crystallised from methanol to give **10**, as colourless plates (yield 0.9 g, 43.2%), m.p. 135°; [ $\alpha$ ]<sub>D</sub> + 65.5° (*c*, 2, pyridine); UV (MeOH): 265, 248; IR (KBr): 3300 (OH); MS: 344 (M<sup>+</sup>); PMR (CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>): 7.90 (*s*, 1H, H-3), 6.2 (*d*, 1H, *J*<sub>1,2'</sub> = 5 Hz, H-1'), 4.80 (*m*, 1H, H-2'), 4.30-4.00 (*m*, 2H, H-3' & H-4'), 3.59 (*m*, 2H, 5'-CH<sub>2</sub>), 2.62 (*s*, 3H, SCH<sub>3</sub>) and 2.55 (*s*, 3H, SCH<sub>3</sub>) (Found: C, 41.6; H, 4.9; N, 15.9. C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> requires C, 41.9; H, 4.7; N, 16.3%).

#### 4-Amino-6-methylthio-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**9**)

Method 1 – A mixture of **8** (4 g, 6 mmol) and methanolic ammonia (80 ml MeOH, saturated with NH<sub>3</sub> at 0°) was heated at 120° in a steel bomb for 24 hr. MeOH and excess of NH<sub>3</sub> were removed under reduced pressure, the residue dissolved in water (100 ml) and extracted with ether (4  $\times$  25 ml). Water from the aqueous extract was removed *in vacuo* and the solid, obtained recrystallised from dry methanol to give **9** as colourless granules (yield 0.8 g, 38.4%), m.p. 240-41°; UV (MeOH): 278, 262; [ $\alpha$ ]<sub>D</sub> + 53° (*c*, 0.05, pyridine); IR (KBr): 3340; MS: 313 (M<sup>+</sup>); PMR (CDCl<sub>3</sub> + DMSO-*d*<sub>6</sub>): 8.01 (*s*, 1H, H-3); 7.52 (*bs*, 2H, NH<sub>2</sub>), 5.95 (*d*, 1H, *J*<sub>1,2'</sub> = 5.0 Hz, H-1'), 5.0-4.3 (*m*, 1H, H-2'), 4.2-3.7 (*m*, 2H, H-3' & H-4'), 3.58-3.10 (*m*, 2H, H-5'), 2.40 (*s*, 3H, SCH<sub>3</sub>) (Found: C, 42.4; H, 4.4; N, 21.9. C<sub>11</sub>H<sub>15</sub>N<sub>5</sub>O<sub>4</sub>S requires C, 42.2; H, 4.8; N, 22.4%).

Method 2 – The arabinoside (**10**) (1.5 g, 4.5 mmol) and methanolic-ammonia (30 ml MeOH, saturated with NH<sub>3</sub> at 0°) was heated at 120° in a

steel bomb for 16 hr. MeOH and excess of  $\text{NH}_3$  were removed under reduced pressure. The product was crystallised from MeOH to give **9** (yield 0.8 g, 90%).

*4-Amino-6-methylsulphonyl-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (12)*

To a solution of **9** (0.5 g, 1.6 mmol) in gl acetic acid (10 ml) protected from light, was added  $\text{H}_2\text{O}_2$  (1.8 ml, 30%). The mixture was kept at ambient temperature for 24 hr, ethanol (10 ml) was added to it and evaporated. The process was repeated 4 times to remove excess of  $\text{H}_2\text{O}_2$ . The crude product obtained was crystallised from cold water to give **12** as white granules (yield 0.1 g, 33%), m.p. 259–60° (d); UV (MeOH): 278, 242, 218; IR (KBr): 1130, 1445 ( $\text{SO}_2\text{CH}_3$ ); MS: 344 ( $\text{M}^+ - 1$ ); PMR ( $\text{DMSO}-d_6$ ): 8.52 (s, 1H, H-3), 7.25 (bs, 2H,  $\text{NH}_2$ ), 6.15 (d, 1H,  $J_{1,2'} = 4.5$  Hz, H-1'), 5.0 (m, 1H, H-2'), 4.25 (m, 2H, H-3' and H-4'), 3.80 (m, 2H, 5'- $\text{CH}_2$ ), 3.60 (s, 3H,  $\text{SO}_2\text{CH}_3$ ).

*4-Amino-6-methoxy-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (14)*

Method 1 – A mixture of **12** (0.3 g, 0.6 mmol), anhyd MeOH (30 ml), MeONa (1 ml) (0.1 g Na in 25 ml abs MeOH) was refluxed for 12 hr., cooled, neutralised with AcOH and evaporated under reduced pressure. The product, obtained was crystallised from water to give **14**, as white granules (yield 0.18 g, 70%), m.p. 245–46°; UV (MeOH): 232, 287;  $[\alpha]_D + 97.8^\circ$  (c, 1.7 pyridine); MS: 297 ( $\text{M}^+$ ); IR (KBr): 3330; PMR ( $\text{DMSO}-d_6$ ): 8.00 (s, 1H, H-3), 7.45 (bs, 2H,  $\text{NH}_2$ ), 5.95 (d, 1H,  $J_{1,2'} = 5$  Hz, H-1'), 4.9–4.6 (m, 1H, H-2'), 4.1–3.85 (m, 2H, H-3' & H-4'), 3.80 (s, 3H,  $\text{OCH}_3$ ), 3.60–3.40 (m, 2H, 5'- $\text{CH}_2$ ) (Found: C, 44.1; H, 5.4; N, 24.0.  $\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_5$  requires C, 44.4; H, 5.0; N, 23.6%).

Method 2 – A mixture of **13** (0.3 g, 0.58 mmol), abs MeOH (30 ml), MeONa (0.65 g Na in 12 ml abs MeOH) was refluxed for 12 hr. The resulting mixture was worked up as above to give **14** (yield 0.14 g, 80%).

*4-Acetamido-6-methylthio-1- $\alpha$ -(2,3,5-tri-O-acetyl-D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (11)*

A mixture of **9** (1 g, 3.2 m mol), anhyd pyridine (15 ml) and  $\text{Ac}_2\text{O}$  (2.5 ml) was kept at room temperature for 12 hr. The resulting mixture was worked-up in the usual way. The crude product thus obtained, was chromatographed on a  $\text{SiO}_2$  (80 g) column. Elution with  $\text{CHCl}_3$ –MeOH (97:3, v/v) afforded **11**, which crystallised from

ethanol as colourless needles (yield 0.8 g, 80%), m.p. 78–79°; UV(MeOH): 235, 278; IR(KBr): 1740 ( $\text{C}=\text{O}$ ); MS: 481 ( $\text{M}^+$ ); PMR ( $\text{CDCl}_3 + \text{DMSO}-d_6$ ): 7.90 (s, 1H, H-3), 6.22 (d, 1H,  $J_{1,2'} = 3$  Hz, H-1'), 5.8–5.6 (m, 1H, H-2'), 5.39–5.1 (m, 1H, H-3'), 4.7–4.5 (m, 1H, H-4'), 4.3–4.1 (m, 2H, 5'- $\text{CH}_2$ ), 2.51 (s, 3H,  $\text{SCH}_3$ ), 2.21, 2.08, 2.02 and 1.95 (each s, 3H,  $\text{COCH}_3$ ) (Found: C, 47.8; H, 4.5; N, 14.2.  $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_8\text{S}$  requires C, 47.4; H, 4.8; N, 14.5%).

*4-Acetamido-6-methylsulphonyl-1- $\alpha$ -(2,3,5-tri-O-acetyl-D-arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (13)*

A mixture of **11** (0.2 g, 0.4 m mol), dil AcOH (10 ml, 50%) and  $\text{KNO}_3$  (0.2 g) at 0° was stirred for 2 hr. To it was added  $\text{H}_2\text{O}_2$  (25 ml, 32%) till the colour disappeared. The resulting mixture was extracted with  $\text{CHCl}_3$ , washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed. The product, thus obtained, was crystallised from EtOH to give **13**, as colourless needles (yield 0.18 g, 75%); m.p. 65°; IR(KBr): 1141, 1320 ( $\text{CH}_3\text{SO}_2$ ); PMR ( $\text{CDCl}_3 + \text{DMSO}-d_6$ ): 8.80 (s, 1H, H-3), 6.32 (d, 1H,  $J_{1,2'} = 2$  Hz, H-1'), 5.90–5.72 (m, 1H, H-2'), 5.32–5.15 (m, 1H, H-3'), 4.80–4.50 (m, 1H, H-4'), 4.30–4.10 (m, 2H, 5'- $\text{CH}_2$ ), 3.5 (s, 3H,  $\text{SO}_2\text{CH}_3$ ), 2.15, 2.00, 1.95 (each s, 3H,  $\text{COCH}_3$ ) (Found: C, 44.6; H, 4.7; N, 14.0.  $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_{10}\text{S}$  requires C, 44.4; H, 4.5; N, 13.7%).

*4-Methoxy-6-methylthio-1- $\alpha$ -D-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (15)*

A mixture of **8** (4 g, 6 m mol) abs MeOH and MeONa (0.7 g, Na in 100 ml abs MeOH) was refluxed for 72 hr. The resulting mixture was cooled, neutralised with AcOH and evaporated under reduced pressure. The crude product, thus obtained, was chromatographed over  $\text{SiO}_2$  (100 g) column. Elution with  $\text{CHCl}_3$ –MeOH (96:4, v/v) afforded **15**, which crystallised from abs MeOH as needles, (yield 0.8 g, 42%); m.p. 275°; UV(MeOH): 240, 279;  $[\alpha]_D + 178.8^\circ$  (c, 0.45, pyridine); IR(KBr): 3200; MS: 328 ( $\text{M}^+$ ); PMR( $\text{DMSO}-d_6$ ): 8.05 (s, 1H, H-3), 5.92 (d, 1H,  $J_{1,2'} = 5$  Hz, H-1'), 4.9–4.5 (m, 1H, H-2'), 4.1–3.8 (m, 2H, H-3' and H-4'), 3.9 (s, 3H,  $\text{OCH}_3$ ), 3.55 (m, 2H, 5'- $\text{CH}_2$ ), 2.51 (s, 3H,  $\text{SCH}_3$ ).

*4-Methoxy-6-methylthio-1- $\alpha$ -(2,3,5-tri-O-acetyl arabinofuranosyl)pyrazolo[3,4-*d*]pyrimidine (16)*

A mixture of **15** (1 g, 3.2 m mol), anhyd pyridine (15 ml) and  $\text{Ac}_2\text{O}$  (2.5 ml) was stirred at ambient temperature for 12 hr. The resulting mixture was worked up in the usual manner and the pro-

duct crystallised from EtOH to give **16** (yield 0.8 g, 80%); m.p. 125°; IR(KBr): 1750 (C=O); MS: 454 ( $M^+$ ); PMR( $CDCl_3$  + DMSO- $d_6$ ): 7.9 (*s*, 1H, H-3), 6.32 (*s*, 1H,  $J=3$  Hz, H-1'), 6.2-6.0 (*m*, 1H, H-2'), 5.39-5.2 (*m*, 1H, H-3'), 4.68-4.40 (*m*, 1H, H-4'), 4.25-4.10 (*m*, 2H, H-5'), 4.0 (*s*, 3H,  $OCH_3$ ), 2.51 (*s*, 3H,  $SCH_3$ ), 2.05, 2.0, 1.9 (each *s*, 3H,  $COCH_3$ ) (Found: C, 47.8; H, 4.4; N, 12.7.  $C_{18}H_{22}N_4O_8S$  requires C, 47.6; H, 4.8; N, 12.3%).

**4-Methoxy-6-methylsulphonyl-1- $\alpha$ -(2,3,5-tri-*O*-acetyl-*D*-arabinofuranosyl)pyrazolo[3,4-*d*]-pyrimidine (**18**)**

$KMnO_4$  oxidation of **16**, as described for **13**, afforded after usual work-up including column chromatography over  $SiO_2$  column, **18** which crystallised from aq. MeOH (yield 80%); m.p. 90-93°; IR(KBr): 1120, 1450 ( $SO_2CH_3$ ); PMR( $CDCl_3$  + DMSO- $d_6$ ): 8.36 (*s*, 1H, H-3), 6.52 (*d*, 1H,  $J_{1,2'}=3$  Hz, H-1'), 6.15-6.00 (*m*, 1H, H-2'), 5.41-5.25 (*m*, H, H-3'), 4.62-4.48 (*m*, 1H, H-4'), 4.3-4.1 (*m*, 2H, 5'- $CH_2$ ), 4.2 (*s*, 3H,  $OCH_3$ ), 3.39 (*s*, 3H,  $SO_2CH_3$ ), 2.09, 2.02 and 2.0 (each *s*, 3H,  $COCH_3$ ) (Found: C, 44.6; H, 4.3; N, 11.8.  $C_{18}H_{22}N_4O_{10}S$  requires C, 44.4; H, 4.5; N, 11.5%).

**6-Amino-4-methoxy-1- $\alpha$ -*D*-arabinofuranosylpyrazolo[3,4-*d*]pyrimidine (**17**)**

A mixture of **18** (0.3 g, 0.6 mmol) and liquid  $NH_3$  (10 ml) was heated in a steel bomb for 16 hr. Excess of  $NH_3$  was evaporated, the product crystallised from water to afford **17**, as colourless granules (yield 0.15 g, 75%); m.p. 205°;  $[\alpha]_D +151.4^\circ$  (*c*, 0.5 pyridine); PMR(DMSO- $d_6$ ): 8.12 (*s*, 1H, H-3), 7.00 (*bs*, 2H,  $NH_2$ ), 6.15 (*d*, 1H,  $J=5$  Hz, H-1'), 5.10-4.85 (*m*, 1H, H-2'), 4.3-4.0 (*m*, 2H, H-3' & H-4'), 4.20 (*s*, 3H,  $OCH_3$ ), 3.7-3.6 (*m*, 2H, 5'- $CH_2$ ) (Found: C, 44.6; H, 5.4; N, 23.7.  $C_{11}H_{15}N_5O_5$  requires C, 44.4; H, 5.0; N, 23.6%).

**Antiviral assay**

Ranikhet disease virus (RDV) was used for antiviral screening of the compounds. The strain of RDV, the haemagglutination test, the method of preparation of CAM culture and the optimal condition of the infection by the virus are described

in earlier publication<sup>13</sup>. The stationary culture of chriallantoic membrane of 10 to 12 days old chick embryos were prepared from white leg horn eggs.

Aqueous solutions/suspensions (0.1 mg/ml) of **9**, **10**, **12**, **14**, **15** and **17** were incubated to each CAM culture using 6 CAM culture sample along with 0.064 HA/ml of RDV. The culture were incubated at 37° for 48 hr. The percentage inhibition of virus multiplication was assayed from the HA titre of the nutrient fluid of CAM culture infected with RDV. Only **12** and **17** exhibited 70 and 50% inhibition and the other compounds exhibited either weak activity or were found inactive.

**Acknowledgement**

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## Structure of a Glucan Isolated from Tal Fruit (*Borassus flabellifer*)

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Saponification of the aqueous extract from the juice of the mesocarp of Tal fruit (*Borassus flabellifer*) furnishes a mixture of polysaccharides containing GalA (53%), Glc (25%), Gal (3.1%), Ara (2.6%), Xyl (2.2%), and Rha (1.5%). Pectinase treatment followed by gel filtration chromatography of the crude polysaccharide mixture yields a pure glucan (BF-B<sub>2</sub>) containing 96.2% Glc. Methylation analysis, periodate oxidation and Smith degradation studies on BF-B<sub>2</sub> indicate it to be a (1 → 6)-linked glucan having branching at O-3 of every tenth glucosyl residue. A plausible structure (I) has been suggested for the average repeating unit of the glucan.

Earlier it was reported<sup>1</sup> that the juice of *Borassus flabellifer* (commonly known as Tal fruit) contained a pectic substance (BF-A). Saponification of BF-A yielded BF-B, which contained GalA (53%) and Glc (25%) along with minor components like Gal (3.1%), Ara (2.6%), Xyl (2.2%) and Rha (1.5%). It was also mentioned in that report that the glucosyl residues of BF-B constituted a separate glucan which remained associated with the polygalacturonan. We report herein the isolation and structure of the pure glucan.

As per previous report<sup>1</sup>, the crude pectinase (*vide infra*) used in that investigation could completely depolymerise not only pectic acids (irrespective of their having different insertions and/or substitutions) but also the associated galactans, arabinans and starch. In order to elaborate this finding and isolate the pure glucan, BF-B was prepared as described earlier<sup>1</sup>. For further purification, an aq. solution (0.1%) of BF-B was subjected to high speed centrifugation (15,000 rpm, 30 min, 5°) and the carbohydrate material (BF-B) isolated from the supernatant liquor. A portion of BF-B was then treated with pectinase under appropriate conditions. Two control experiments, (a) containing only potato starch and (b) containing a mixture of BF-B and potato starch, were also run simultaneously. The enzyme was deactivated and the three reaction mixtures separately dialysed. Analysis of the dialysate from BF-B alone (*vide supra*) showed the presence of GalA, Gal and Ara but no Glc, whereas similar analysis of the dialysates from the control experiment (a) showed the presence of Glc and that from (b) showed the presence of Glc in addition to GalA, Gal and Ara. This finding substantiated the earlier contention that the glucan portion of BF-B had a structure different from starch and as such, the glucan portion should be isolable from the pectinase digest.

BF-B (68.5 mg) was then treated with pectinase. The reaction mixture was dialysed and the bag con-

tent lyophilised to yield BF-B<sub>1</sub>. The latter (BF-B<sub>1</sub>) was enriched in hexose (68.8%) but it still contained GalA (20.9%). A repetition of the pectinase treatment of BF-B<sub>1</sub> yielded polysaccharide BF-B<sub>2</sub> which contained only Glc (96.2%) and had  $[\alpha]_{589.5} + 198^\circ$ . BF-B<sub>2</sub> did not give any colouration with iodine solution. Chromatography of BF-B<sub>2</sub> on a column (2.5 × 65 cm) of Sephadex G-150 gave only one peak responding positively to phenol-H<sub>2</sub>SO<sub>4</sub> reaction<sup>2</sup>. It contained only glucose in about the same proportion as its precursor. Hence, BF-B<sub>2</sub> was identified to be a pure glucan.

In order to find out the positions of various linkages, BF-B<sub>2</sub> was methylated first by the Kuhn's method<sup>3</sup> (twice) and then by Hakomori method<sup>4</sup> (once). The resulting permethylated product showed no -OH band in its IR spectrum and had  $[\alpha]_{589.5} + 19.3^\circ$ . A portion (~ 1 mg) of the premethylated BF-B<sub>2</sub> was formylated<sup>5</sup> and hydrolysed. The hydrolysate was converted into the alditol acetate and analysed by GLC and GLC-MS. This revealed the presence of 2,3,4,6-tetra-, 2,3,4-tri- and 2,4-di-O-methylglucose in the respective molar proportions of 1:9.2:1.02 (cf Table 1). From the methylation analysis data, it may be concluded that the glucan has a backbone consisting of →6)-Glc-(1→ units with branching at O-3 of every tenth glucosyl residue. Hence, a plausible structure (I) was proposed for the average repeating unit of the glucan.

Further support in respect of the structure (I) was obtained from periodate oxidation studies<sup>6</sup>. BF-B<sub>2</sub>

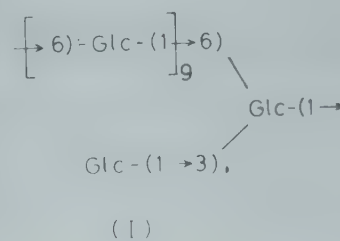


Table 1—GLC-MS and GLC Analyses of Alditol Acetate Derivatives of Methylated BF-B<sub>2</sub>

Components (as alditol acetates of glucose)	RRT*		Mol ratio†	Major mass fragments	Nature of linkage
	column-I	column-II			
2,3,4,6-Me <sub>4</sub>	1.06	1.00	1	55,71,87,101,117	Glc-p-(1 →
	(1.00)	(1.00)		129,145,161,205	
2,3,4-Me <sub>3</sub>	2.52	2.20	9.2	58,71,87,101,117	→ 6)-Glc-p-(1 →
	(2.49)	(2.22)		129,161,189,233	
2,4-Me <sub>2</sub>	5.4	4.15	1.02	58,87,117,129	→ 3,6)-Glc-p-(1 →
	(5.10)	(4.21)		139,159,189	

\* Relative retention time with respect to that of 1,5-di-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucitol as unity. Values in parentheses are recorded from literature<sup>10</sup>.

† From GLC (column-I)

reduced 1.6 mol (required 1.8 mol) of the oxidant and liberated 0.81 mol (required 0.9) of formic acid per anhydrohexose unit. Smith degradation of BF-B<sub>2</sub> furnished substantial amount of glycerol and some glucose. The survival of some glucose and formation of glycerol corroborated the proposed structure.

### Experimental Procedure

PC was carried out on Whatman No. 1 paper sheets using the solvent systems (v/v): (A) EtOAc-C<sub>5</sub>H<sub>5</sub>N-H<sub>2</sub>O (8:2:1), (B) EtOAc-C<sub>5</sub>H<sub>5</sub>N-AcOH-H<sub>2</sub>O (5:5:1:3), and (C) *n*-BuOH-AcOH-H<sub>2</sub>O (3:1:1). Staining reagents used were (i) alkaline silver nitrate and (ii) benzidine-periodate.

Neutral sugars were estimated by phenol-H<sub>2</sub>SO<sub>4</sub> method<sup>2</sup> or L-cysteine-H<sub>2</sub>SO<sub>4</sub> method<sup>7</sup> and also by GLC of their alditol acetates using *myo*-inositol as internal standard. Uronic acid was estimated by the carbazole-H<sub>2</sub>SO<sub>4</sub> method<sup>8</sup>. All evaporations were performed below 40° under reduced pressure.

GLC was performed on glass columns (1.83 × 6 mm) containing (I) 3% ECNSS-M on gas chrom Q(100-120 mesh) at 190° (for alditol acetates of neutral sugars) and at 170° (for alditol acetates of partially methylated neutral sugars), and (II) 3% OV-225 on SIL-RUB (80-100 mesh) at 170° (for alditol acetates of partially methylated neutral sugars). GLC-MS analysis was conducted as reported earlier<sup>5</sup>.

Pectinase (polygalacturonase; poly α-1, 4-galacturonide glucuronohydrolase; EC. No. 3.2.1.15; from *Aspergillus niger*) was purchased from Sigma Chemical Company, USA.

### Isolation of the Tal fruit polysaccharide (BF-A)

The skin-free mesocarp of Tal fruit (500 g) was mashed with water and the semi-fluid mass (also containing fibres) suspended in a double walled nylon bag. The yellowish viscous juice that oozed out of the bag, was diluted with water (1 vol). To this solution

ethanol (3 vol) was added under stirring condition to yield a greyish yellow precipitate (BF-A, 2.6 g).

### Saponification of BF-A

BF-A (2.6 g) was dispersed in potassium hydroxide solution (0.1 M, 200 ml) under nitrogen and the reaction mixture left overnight at room temperature. The turbid solution was centrifuged (6000 rpm, 10°, 30 min) and the clear supernatant liquor neutralised with cold acetic acid (4N). The polysaccharide (BF-B, ~ 1.5 g) was precipitated from this solution by addition of ethanol (3 vol). BF-B contained GalA (53%), Glc (25%) and some minor components, viz. Gal (3.1%), Ara (2.6%), Xyl (2.2%) and Rha (1.5%).

### Pectinase treatment of BF-B and control substrates

To a dispersion of Bf-B (~ 5 mg) in sodium acetate buffer (0.1 M, 5 ml, pH 4), pectinase (~ 1 mg) was added and the mixture left for 24 hr at 25° under a drop of toluene. Two control experiments containing (a) potato starch (~ 3 mg) and (b) a mixture of potato starch and BF-B (3 mg each) were run simultaneously with pectinase under the same conditions. The enzyme was deactivated (80°, 15 min) and the three reaction mixtures were separately dialysed and the dialysates decationised and lyophilised. The residues were examined by PC (solvent A, staining reagent i). The residue from BF-B did not furnish any Glc but that from both (a) and (b) yielded Glc.

### Isolation of pure glucan (BF-B<sub>2</sub> from BF-B)

A dispersion of BF-B (68.5 mg) in sodium acetate buffer (0.1 M, 200 ml, pH 4) was centrifuged (15,000 rpm, 5°, 30 min). Pectinase (~ 5 mg) was added to the clear supernatant liquor and the mixture kept for 24 hr at 25° under a few drops of toluene. The enzyme was deactivated and the cooled solution centrifuged. The centrifugate was extensively dialysed. The bag content was worked up to yield BF-B<sub>1</sub> was subjected

to a second pectinase treatment and the reaction mixture, after usual work-up yielded BF-B<sub>2</sub> (10.2 mg) which contained only Glc (96.2%) and had  $[\alpha]_{589.5} + 198^\circ$ . The process of isolation of the pure glucan (BF-B<sub>2</sub>) from BF-B was repeated several times.

*Gel filtration of the pure glucan (BF-B<sub>2</sub>) through a column of Sephadex G-150*

An aq. solution (0.7 ml) of BF-B<sub>2</sub> (33.1 mg) was run through a column (2.5 × 65 cm) of Sephadex G-150. The column was eluted with water and fractions of 4 ml each were collected at the rate of 12 ml/hr and monitored by phenol-H<sub>2</sub>SO<sub>4</sub> colour reaction<sup>2</sup>. This furnished only one peak (fraction numbers 23-34). The fractions 23-34 were pooled and the carbohydrate material (BF-B<sub>2</sub>) isolated by lyophilisation (25.8 mg). Analysis showed that the resulting preparation was identical with the precursor.

*Methylation analysis of the glucan (BF-B<sub>2</sub>)*

Dry BF-B<sub>2</sub> (3 mg) was subjected to methylation by the method of Kuhn<sup>3</sup> as reported earlier<sup>5</sup>. The product still showed a weak —OH band in its IR spectrum. This was further methylated by Hakomori method<sup>4</sup> as described earlier<sup>5</sup>. The resulting permethylated product (3.5 mg) showed no —OH band in its IR spectrum. A portion of the permethylated material (~1 mg) was formolysed and hydrolysed<sup>5</sup> and then subjected to GLC-MS analyses (cf Table 1).

*Periodate oxidation and Smith degradation of the glucan (BF-B<sub>2</sub>)*

A solution of BF-B<sub>2</sub> (2 mg/ml, in duplicate) was oxidised with sodium metaperiodate (0.04 M) in the dark at 4° as described earlier<sup>9</sup>. The periodate uptake<sup>6</sup> became constant in about 170 hr corresponding to the

reduction of 1.8 mol of the oxidant per anhydro hexose unit. After the completion of oxidation, an aliquot (5 ml) of the reaction mixture was treated with ethylene glycol (50 µl) and after 15 min, the liberated formic acid titrated by standard NaOH. The liberation of one mol of formic acid corresponded to the oxidation of 0.8 mol of the hexose units of BF-B<sub>2</sub>. After titration, the pooled reaction mixture was extensively dialysed and the bag content concentrated. The oxidised carbohydrate material was reduced with KBH<sub>4</sub>. After usual work-up the resulting residue was hydrolysed with 1% trifluoroacetic acid (1 ml) for 10 hr at 100°. The hydrolysate was worked-up in the usual way and the product acetylated. GLC analysis (Programming<sup>5</sup>) of the product furnished glycerol and glucitol.

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## Copolymerization of $\epsilon$ -Carbobenzoxy L-Lysine & L-Valine NCA's: Sequence Length Distribution & Conformation

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The correlation of sequence length distribution analysis of the copolymers of  $\epsilon$ -carbobenzoxy-L-lysine (K) and L-valine (V) with their solid state conformation is reported.

Large number of random copolypeptides synthesised from the corresponding N-carboxy- $\alpha$ -amino acid anhydrides (NCA's) have been used as protein models in understanding the relation between composition and conformational parameters<sup>2-5</sup>. The usual procedure in these studies has been to copolymerize various amino acid N-carboxy anhydrides to about 100% conversion, isolate the copolypeptide and then determine the average amino acid composition of the copolymer and carry out the conformational studies. However, little attention was paid to the copolymerization conditions and the reactivity of the comonomers.

Shalitin and Katchalski<sup>6</sup> have shown that due to a difference in reactivity ratios, polymerization of the  $\gamma$ -benzyl-L-glutamate,  $\epsilon$ -N-carbobenzoxy-L-lysine system results in copolymers which are rich in glutamate in the early stage of reaction (10% conversion). Similar results were obtained for  $\gamma$ -benzyl-L-glutamate, L-leucine<sup>7</sup> copolymers,  $\gamma$ -methyl-L-glutamate,  $\epsilon$ -carbobenzoxy-L-lysine<sup>8</sup> copolymers and  $\gamma$ -benzyl-L-glutamate, valine<sup>9</sup> copolymers, where the glutamate NCA in each case was more reactive and at low conversions resulted in copolymers whose glutamate composition was higher than that in the original monomer mixture.

The probability of sequence length distribution determined from reactivity ratios would be expected to help in predicting the most probable primary structure of random copolypeptide. The present paper describes the sequence length distribution analysis and solid state conformation of copolymers of  $\epsilon$ -carbobenzoxy-L-lysine (K) and L-valine (V). These studies were carried out in order to verify the role of these amino acids in dictating a specific conformation.

### Materials and Methods

#### *Preparation and composition of copolymers*

The copolymers were prepared in dioxane and

benzene-methylene chloride as described earlier<sup>10</sup> starting with initial feed of K:V = 80:20, 50:50 and 20:80. The copolymerization was allowed to proceed to 10% conversion. The composition of copolymers was determined by PMR spectra by measuring the relative integrated area of phenyl protons of carbobenzoxy group of K (at  $\delta$  7.20-7.45) and of the six protons of dialkyl group of valine (at  $\delta$  1.05). The compositions of the copolymers determined by this method were found to be K:V=80:20, 47:53 and 35:65 in dioxane and 80:20, 52:48 and 32:68 in benzene-methylene chloride.

#### *IR Spectra*

The IR spectra were recorded in films on a Perkin-Elmer B 58 grating spectrophotometer. The films were cast from the dilute solution of copolypeptide in chloroform containing 5% TFA on the clear surface of sodium chloride crystal.

#### *CD Spectra*

The CD spectra were recorded in films on a Jasco spectropolarimeter model J-500A. The films were cast from the dilute solution of copolypeptide in chloroform containing 5% TFA on the quartz plate.

### Results and Discussion

#### *Sequence length distribution*

Sequence length distributions of the two amino acids in the copolypeptides were calculated as a function of initial feed composition of monomers using the reactivity ratio values calculated by the author<sup>10</sup> as described in the literature<sup>11</sup>.

The probability of occurrence of a sequence of monomer was plotted as a function of number of amino acid residues (n) in the form of a histogram, the results of which are as follows:

For the copolymer prepared in dioxane with 50:50 feed the probability of the occurrence of K sequence was similar to that of V sequence; and the long sequences with  $n \neq 6$  of either K or V were not favoured. While sequences with  $n > 4$  of either K or V had low probability for the copolymer prepared in benzene-methylene chloride the copolymers prepared in both the solvents with initial feed K:F=80:20 had the probability of occurrence of heptameric blocks of K residues but valyl residues occurred mostly as single units ( $\sim 80\%$ ); this situation was more or less reversed when the composition of the feed was reversed (K:V=20:80). The above analysis indicated that there were significant differences in sequence length distribution of copolymers formed at low conversion carrying feed composition.

#### Solid state conformation of copolymers

IR and CD spectra of these copolymers are shown in Figs 1, and 2 respectively. The IR spectrum of copoly ( $\epsilon$ -Cbz-L-lysine<sup>80</sup>-L-valine<sup>20</sup>), prepared in dioxane, exhibited the amide-I band at 1659 with a hump at 1630 and the amide-II band

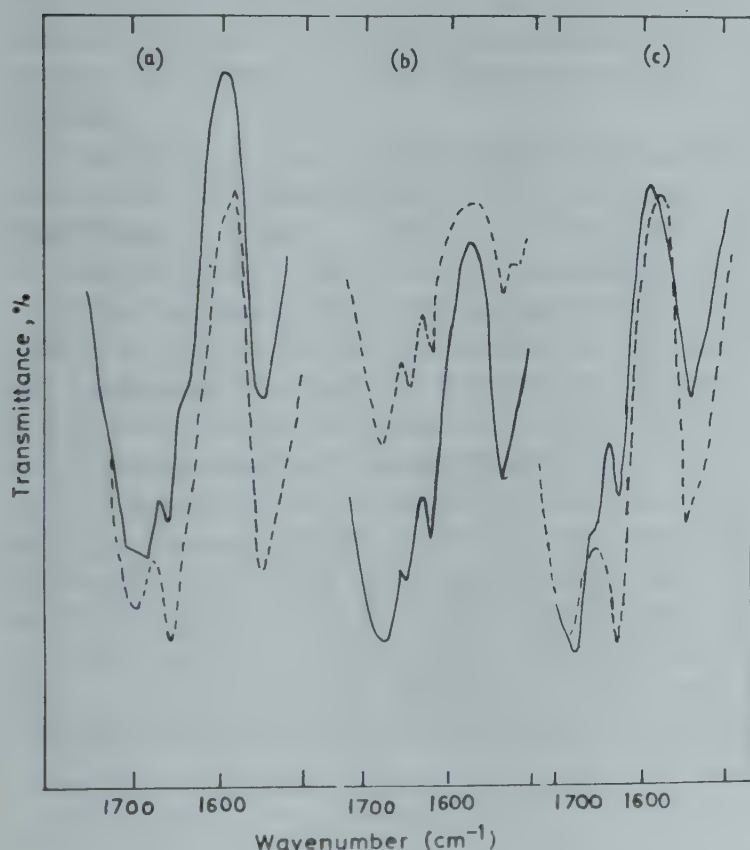


Fig. 1—IR (film) spectra of copolypeptides in the amide-I and amide-II regions (a) poly[Lys(Cbz)<sup>80</sup>-Val<sup>20</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>80</sup>-Val<sup>20</sup>] prepared in benzene-methylene chloride (---); (b) poly[Lys(Cbz)<sup>47</sup>-Val<sup>53</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>52</sup>-Val<sup>48</sup>] prepared in benzene-methylene chloride (---) and (c) poly[Lys(Cbz)<sup>35</sup>-Val<sup>65</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>42</sup>-Val<sup>58</sup>] prepared in benzene-methylene chloride (---).

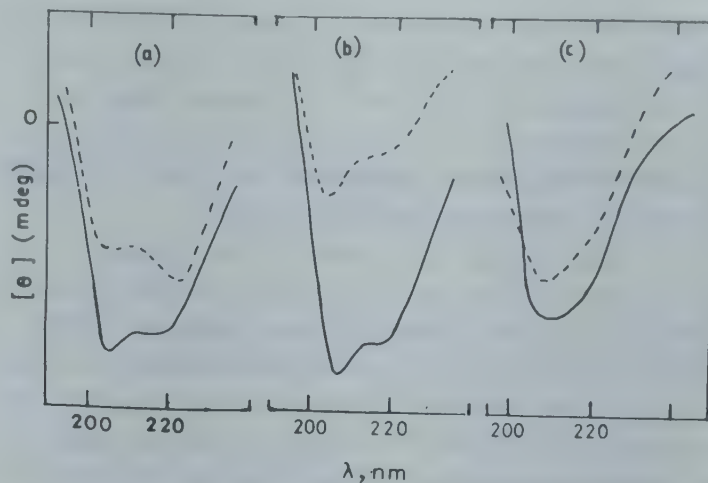


Fig. 2—CD (film) spectra of copolypeptides (a) poly[Lys(Cbz)<sup>80</sup>-Val<sup>20</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>80</sup>-Val<sup>20</sup>] prepared in benzene-methylene chloride (---), (b) poly[Lys(Cbz)<sup>47</sup>-Val<sup>48</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>47</sup>-Val<sup>48</sup>] prepared in benzene-methylene chloride (---) and (c) poly[Lys(Cbz)<sup>35</sup>-Val<sup>65</sup>] prepared in dioxane (—), poly[Lys(Cbz)<sup>32</sup>-Val<sup>68</sup>] prepared in benzene-methylene chloride (---).

at 1547  $\text{cm}^{-1}$ . But the copolymers prepared in the mixed solvent showed the amide-I and amide-II bands at 1655 and 1527  $\text{cm}^{-1}$  respectively in their IR spectra. The CD spectra showed the  $\pi$ - $\pi^*$  and  $n$ - $\pi^*$  transitions at 205 and 220 nm. This suggested the helical structure as the major conformational component along with small beta-component in the two copolymers. This is in agreement with the sequence length distribution analysis indicating a high probability for long lysyl blocks.

The IR spectra of copoly ( $\epsilon$ -Cbs-L-lysine<sup>47</sup>-L-valine<sup>53</sup>) prepared in dioxane and copoly ( $\epsilon$ -Cbz-L-lysine<sup>52</sup>-L-valine<sup>48</sup>) prepared in benzene-methylene chloride with a 1:1 feed, displayed the amide-I bands characteristic of both helical and beta structures (Fig. 1b), but the amide-II band was resolved only for the system prepared in the mixed solvent. The CD spectra of the two systems exhibited helical  $n$ - $\pi^*$  and  $\pi$ - $\pi^*$  bands (Fig. 2b). However, the  $n$ - $\pi^*$  band (218 nm) of the copolymer prepared in the mixed solvent was shallower than that of the other copolymer. This suggests a lesser degree of helical order in the copolymer prepared in the mixed solvent.

The sequence length distribution analysis for a 1:1 feed indicated the pentameric valyl as well as lysyl sequences to be equally feasible. While the Chou-Fasman<sup>12</sup> proclivity for lysyl residue to be in helical conformation ( $p_\alpha$ ) is 1.07, the value for valyl residue is 1.14. Valyl residues are strong beta sheet former  $p_\beta$  for valine being 1.65, whereas for lysine it is only 0.75. Again, valyl residues are reported to induce neighbouring lysyl and protected lysyl residues, as in the polypeptides with defined sequence like Lys-Val-Lys<sup>13,14</sup> or Val-Val-Lys<sup>15</sup>, to adopt

beta conformation. But the present data on random copolypeptides indicate that this is not necessarily so, as helical segments are also present along with a beta-component in the copolymers. Notably, poly- $\epsilon$ -Cbz-L-lysine is not known to form beta structure unlike the deprotected poly-L-lysine.

The IR spectra of copoly( $\epsilon$ -Cbz-L-lysine<sup>32</sup>-L-valine<sup>68</sup>) prepared in mixed solvent and of copoly( $\epsilon$ -Cbz-L-lysine<sup>35</sup>-L-valine<sup>65</sup>) prepared in dioxane exhibited the amide-I band at 1633 characteristic of beta-structure and the amide-II band of the L-valyl rich polymers at 1552  $\text{cm}^{-1}$ . The CD spectra (Fig. 2c) of these copolymers had one minimum at 210-212 nm. But for copoly( $\epsilon$ -Cbz-L-lysine<sup>32</sup>-L-valine<sup>68</sup>) prepared in mixed solvent showed a small hump at 217 nm. This is also in agreement with the sequence length distribution.

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## Syntheses of Sandwicoline & Its Diastereomers

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Sandwicine, isosandwicine, ajmaline and isoajmaline have been reduced and methylated with  $\text{NaBH}_4$  and formic acid/formaldehyde respectively, to yield 21-monohydro- $\text{N}^4$ -methylsandwicine (**2**) (sandwicoline), 21-monohydro- $\text{N}^4$ -methylisosandwicine (**4**), 21-monohydro- $\text{N}^4$ -methylajmaline (**6**) and 21-monohydro- $\text{N}^4$ -methylisosandwicine (**8**) respectively.

Recent work on the alkaloidal constituents of the roots of *Rauwolfia serpentina* Benth resulted in the isolation and synthesis of a new alkaloid sandwicoline<sup>1</sup>. Keeping in view the pharmacological importance of *Rauwolfia* alkaloids<sup>2-8</sup>, it was considered of interest to extend the synthetic studies to the alkaloids isosandwicine, ajmaline and isoajmaline in order to prepare three possible diastereomers of sandwicoline.

Thus, were prepared 21-monohydro- $\text{N}^4$ -methylsandwicine (**2**) (sandwicoline) 21-monohydro- $\text{N}^4$ -methylisosandwicine (**4**), 21-monohydro- $\text{N}^4$ -methylajmaline (**6**) and 21-monohydro- $\text{N}^4$ -methylisosandwicine (**8**) by the sodium borohydride reduction of sandwicine, isosandwicine ajmaline and isoajmaline, respectively followed by methylation of the corresponding reduced products (**1**, **3**, **5** and **7**) with formic acid/formaldehyde.

Melting points were recorded in glass capillaries and are uncorrected. UV spectra were recorded in methanol on UV 240 spectrophotometer and IR spectra in chloroform on JASCO A-302 infrared spectrophotometer. PMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker WP 100 SY FT NMR spectrometer and mass spectra on Varian MAT-112 and

Mat-312 double focussing spectrometers connected to PDP 11/34 computer system.

### Dihydrosandwicine (**1**)

To a solution of sandwicine (0.5 g) in methanol (100 ml), sodium borohydride (1 g) was gradually added with stirring. After keeping it at room temperature for 3 hr, excess of borohydride was destroyed by adding 10% acetic acid, the reaction mixture basified with 20% aq ammonium hydroxide and extracted with ethyl acetate. Usual work-up of the ethyl acetate layer afforded **1** as a crystalline residue (yield theoretical) which recrystallized from acetone in hexagonal rods, m.p.  $210-12^\circ$ ,  $[\alpha]_D^{20} + 102^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 72.9; H, 8.5; N, 8.6; O, 10.0.  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$  requires C, 73.2; H, 8.5; N, 8.5; O, 9.8%); HRMS (rel. int. %):  $m/z$  328.21631 [ $\text{M}^+$ , Calc. for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ , 328.21506 (41)]; IR: 3345, 1370, 3100 and  $1455\text{ cm}^{-1}$ ; UV: 288 and 246 nm.

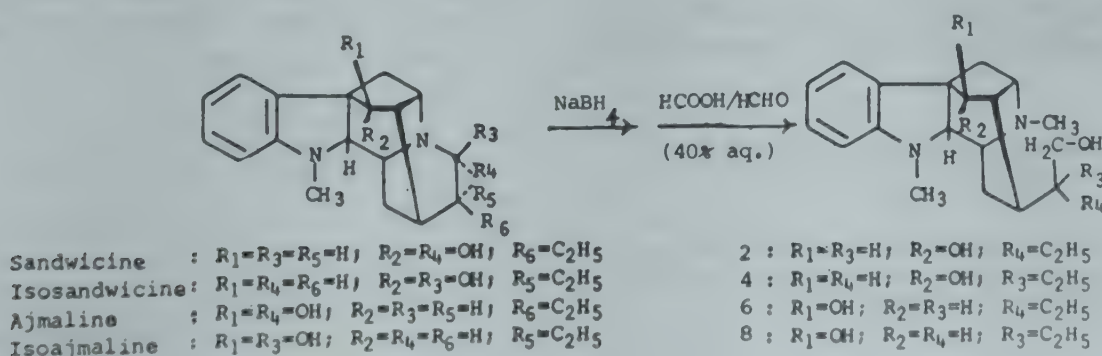
### 21-Monohydro- $\text{N}^4$ -methylsandwicine (**2**)

Dihydrosandwicine (**1**, 0.4 g) was refluxed with 40% aq formic acid (2.4 mol) and formaldehyde (2.4 mol, 40% solution) for 2 hr on a boiling water-bath. The reaction mixture was basified with ammonia and the liberated base extracted with ethyl acetate, the organic layer washed with water, dried and freed of the solvent to afford **2** as a whitish residue, which recrystallized from methanol as elongated rods. Its physical and spectral data were identical in all respects with those of sandwicoline<sup>1</sup>.

Similar reaction conditions were maintained for the syntheses of 21-monohydro- $\text{N}^4$ -methylisosandwicine (**4**), 21-monohydro- $\text{N}^4$ -methylajmaline (**6**), and 21-monohydro- $\text{N}^4$ -methylisoajmaline (**8**).

### Dihydroisosandwicine (**3**)

It was obtained as a crystalline residue (yield theoretical) by  $\text{NaBH}_4$  reduction of isosandwicine as



above; it recrystallized from chloroform-acetone as hexagonal rods, m.p. 172-173°C,  $[\alpha]_D^{20} + 117^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 72.9; H, 8.5, N, 8.6; O, 10.0.  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$  requires C, 73.2; H, 8.5; N, 8.5; O, 9.8%); HRMS (rel. int. %):  $m/z$  328.2163 [ $\text{M}^+$ , Calc. for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ , 328.21506 (41)]; IR: 3346, 1375, 3105 and 1460  $\text{cm}^{-1}$ ; UV: 269 and 248 nm.

#### 21-Monohydro- $N^4$ -methylisosandwicine (4)

Methylation of **3** as described for **2** afforded **4** as a white crystalline residue, which recrystallized from methanol as irregular plates, m.p. 186-87°C;  $[\alpha]_D^{20} = +213^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 73.5; H, 9.0; N, 8.3; O, 9.3.  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$  requires C, 73.7; H, 8.8; N, 8.2; O, 9.4%); HRMS (rel. int. %):  $m/z$  342.2313 [ $\text{M}^+$ , Calc. for  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$ , 342.2307 (13)], 269.1650 ( $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$ )<sup>+</sup> (8), 198.1492 ( $\text{C}_{11}\text{H}_{20}\text{NO}_2$ )<sup>+</sup>, 144.0812 ( $\text{C}_{10}\text{H}_{10}\text{N}$ )<sup>+</sup> (14); IR: 3360, 3110, 1460, 1370  $\text{cm}^{-1}$  (aromatic vibration); UV: 292, 255 and 2100 nm; PMR:  $\delta$  7.14-6.67 (4H, *m*, aromatic protons), 4.78 (1H, *d*,  $J=9.0$  Hz, H-17), 3.52 (1H, *d*,  $J=1.5$  Hz, H-21), 3.49 (1H, *d*,  $J=4.0$  Hz, H-21), 2.82 (3H, *s*,  $\text{N}_1\text{-CH}_3$ ), 2.54 (3H, *s*,  $\text{N}_4\text{-CH}_3$ ), 1.33 (2H, *m*, H-19) and 1.0 (3H, *t*,  $J=7.0$  Hz, H-18).

#### Dihydroajmaline (5)

$\text{NaBH}_4$  reduction of ajmaline afforded **5** in theoretical yield, which recrystallized from chloroform-methanol (1 : 1) as irregular plates, m.p. 171-72°C;  $[\alpha]_D^{20} + 158^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 72.9; H, 8.4; N, 8.7; O, 10.0.  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$  requires C, 73.2; H, 8.5; N, 8.5; O, 9.8%); HRMS (rel. int. %):  $m/z$  328.21632 [ $\text{M}^+$ , Calc. for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ , 328.21507 (41)]; IR: 3346, 1375, 3105 and 1465  $\text{cm}^{-1}$ ; UV: 288 and 246 nm.

#### 21-Monohydro- $N^4$ -methylajmaline (6)

It was obtained as crystalline solid by the methylation of **5** and it recrystallized from chloroform-methanol (1 : 1) as sharp needles, m.p. 181-82°C;  $[\alpha]_D^{20} + 140^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 73.5; H, 8.9; N, 8.3; O, 9.3.  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$  requires C, 73.7; H, 8.8; N, 8.2; O, 9.4%); HRMS (rel. int. %):  $m/z$  342.2318 [ $\text{M}^+$ , Calc. for  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$ , 342.2307 (17)], 269.1654 ( $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$ )<sup>+</sup> (13), 198.1497 ( $\text{C}_{11}\text{H}_{20}\text{NO}_2$ )<sup>+</sup> (100), 168.1395 ( $\text{C}_{10}\text{H}_{18}\text{NO}$ )<sup>+</sup> (19) and 144.0816 ( $\text{C}_{10}\text{H}_{10}\text{N}$ )<sup>+</sup> (16); IR: 3365, 3105, 1465, 1360  $\text{cm}^{-1}$ ; UV: 295.210 and 210 nm; PMR:  $\delta$  7.46-6.63 (4H,

*m*, aromatic protons), 4.42 (1H, *d*,  $W_{1/2}=0.5$  Hz, H-17), 3.21 (2H, *d*,  $J=6.0$  Hz, H-21), 2.79 (3H, *s*,  $\text{N-CH}_3$ ), 2.40 (3H, *s*,  $\text{N}_4\text{-CH}_3$ ), and 1.46 (2H, *m*, H-19), and 0.96 (3H, *t*,  $J=7.0$  Hz, H-18).

#### Dihydroisoajmaline (7)

It was obtained as fine crystallize (yield theoretical) by  $\text{NaBH}_4$  reduction of isoajmaline. It was recrystallized from chloroform-acetone as sharp needles, m.p. 151-52°C;  $[\alpha]_D^{20} + 137^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 72.8; H, 8.5; N, 8.7; O, 10.0.  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$  requires C, 73.2; H, 8.5; N, 8.5; O, 9.8%); HRMS (rel. int. %):  $m/z$  328.21631 [ $\text{M}^+$ , Calc. for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$ , 328.21506 (41)]; IR: 3346, 1375, 3105 and 1460  $\text{cm}^{-1}$ ; UV: 288 and 246 nm.

#### 21-Monohydro- $N^4$ -methylisoajmaline (8)

It was obtained as crystalline solid by the methylation of **7** and it formed irregular plates on recrystallization from chloroform-methanol (1 : 1), m.p. 253-54°C;  $[\alpha]_D^{20} = +81^\circ$  ( $\text{CHCl}_3$ ) (Found: C, 73.5; H, 9.0; N, 8.3; O, 9.3.  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$  requires C, 73.7; H, 8.8; N, 8.2; O, 9.4%). HRMS (rel. int. %):  $m/z$  342.2310 [ $\text{M}^+$ , Calc. for  $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_2$ , 342.2307 (16)], 269.1658 ( $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$ )<sup>+</sup> (13), 198.1489 ( $\text{C}_{11}\text{H}_{20}\text{NO}_2$ )<sup>+</sup> (100), 168.1390 ( $\text{C}_{10}\text{H}_{18}\text{NO}$ )<sup>+</sup> (20) and 144.0811 ( $\text{C}_{10}\text{H}_{10}\text{N}$ )<sup>+</sup> (13); IR: 3350, 3100, 1455, 1375  $\text{cm}^{-1}$ ; UV: 295, 250 and 210 nm; PMR:  $\delta$  7.08-6.78 (4H, *m*, aromatic protons), 4.38 (1H, *d*,  $W_{1/2}=0.5$  Hz, H-17), 3.21 (1H, *d*,  $J=4.0$  Hz, H-21), 3.01 (1H, *d*,  $J=1.5$  Hz, H-21), 2.78 (3H, *s*,  $\text{N-CH}_3$ ), 2.41 (3H, *s*,  $\text{N}_4\text{-CH}_3$ ), 1.42 (2H, *m*, H-19) and 1.10 (3H, *t*,  $J=7.0$  Hz, H-18).

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# 2-(1''-Hydroxynaphthalen-2''-yl)-2-(2',4'-dioxo-3',4'-dihydro-2*H*-naphtho[1,2-*b*]pyran-3'-yl)ethylidene: A Minor Product Formed During Cyclisation of 2-Acetyl-1-naphthyl Methyl Carbonate with Base†

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Potassium carbonate-catalysed cyclisation of 2-acetyl-1-naphthyl methyl carbonate (**1**) gives, besides the expected 4-hydroxybenzo[*h*]coumarin (**2**), a minor product which on the basis of high field 2D <sup>1</sup>H-<sup>1</sup>H COSY, DEPT CMR and mass spectral data has been identified as 2-(1''-hydroxynaphthalen-2''-yl)-2-(2',4'-dioxo-3',4'-dihydro-2*H*-naphtho[1,2-*b*]pyran-3'-yl)ethylidene (**3**).

Base-catalysed cyclisation of alkyl O-acetylaryl carbonates provides a useful method for the synthesis of 4-hydroxycoumarins and related compounds. During the cyclisation of 2-acetyl-1-naphthyl methyl carbonate (**1**), one of us in 1948 observed the formation of a minor product (1.8%), highly insoluble in most of the common organic solvents to which no structure could be assigned at that time<sup>1</sup>. We have now established the structure of this product as 2-(1''-hydroxynaphthalen-2''-yl)-2-(2',4'-dioxo-3',4'-dihydro-2*H*-naphtho[1,2-*b*]pyran-3'-yl)ethylidene (**3**) with the help of high-field two dimensional homonuclear chemical shift correlated (<sup>1</sup>H-<sup>1</sup>H COSY)<sup>2</sup>, broad band (BB) proton decoupled, dis-

tortionless enhancement by polarisation transfer (DEPT)<sup>3</sup> CMR, and mass spectral data.

The main points of our structure elucidation are as follows. Presence of a phenolic -OH in **3** has already been established earlier<sup>1</sup> by FeCl<sub>3</sub> test and formation of a monoacetate. Elemental analysis coupled with molecular ion peak at *m/z* 380 gave the molecular formula as C<sub>25</sub>H<sub>16</sub>O<sub>4</sub> which was further confirmed by observation of 16 protons and 25 carbons in high resolution(400 MHz) PMR and BB decoupled (100.57 MHz) CMR spectra.

Mass fragmentation of **3** supported the proposed structure. The PMR and CMR data were in good agreement with the structure **3**. Noteworthy observations in the CMR spectra were the upfield

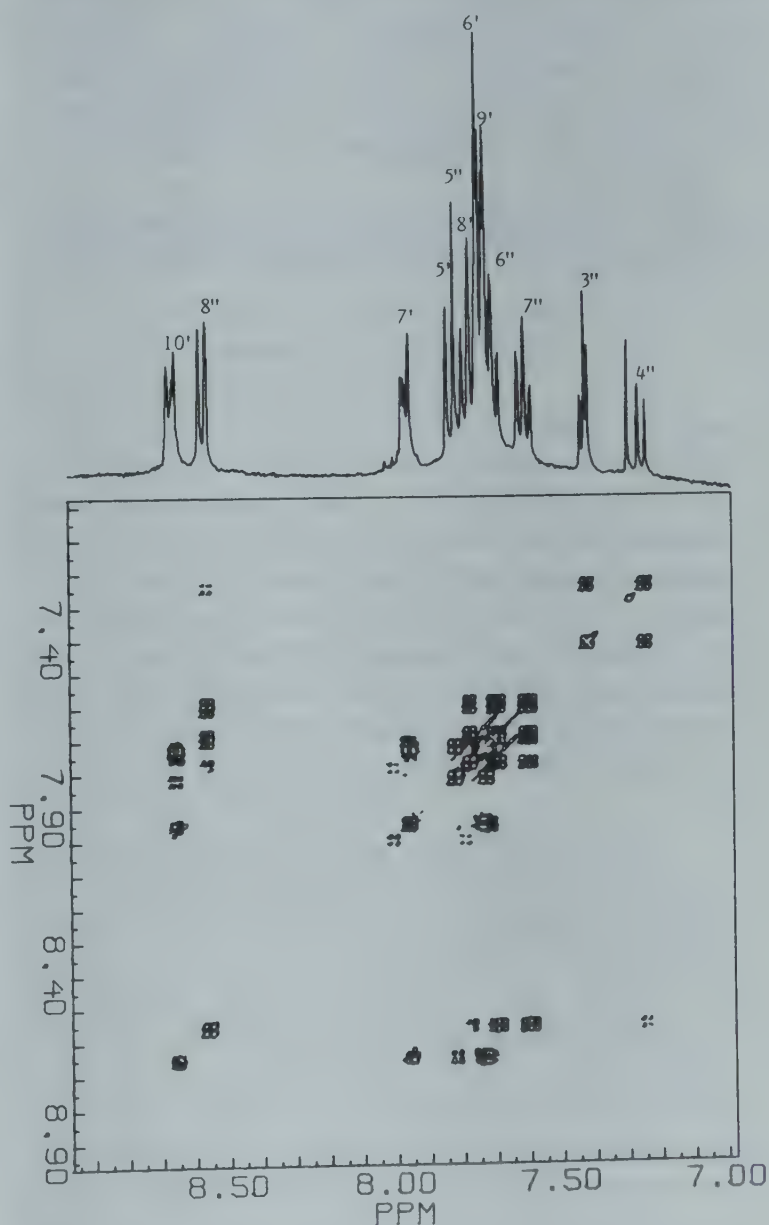
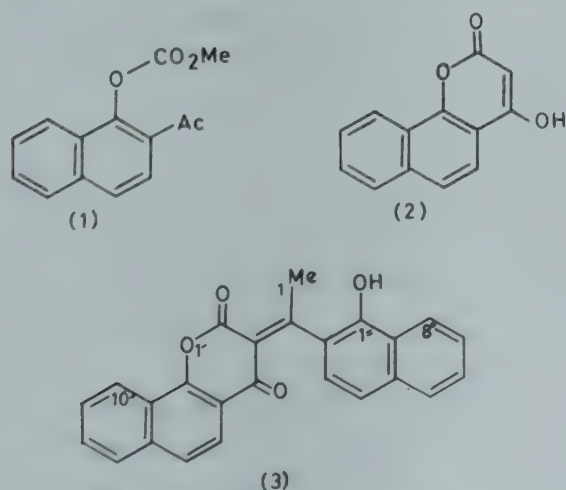


Fig. 1—A section of the contour plot of 2D <sup>1</sup>H-<sup>1</sup>H COSY spectrum of **3** in CDCl<sub>3</sub>, PMR spectrum of this section is shown above the 2D spectrum

shift of C-1" resonance at  $\delta$  149.6 in acetate of **3** compared to 154.4 in the parent compound, and the presence of two carbonyl carbons at  $\delta$  197.6 (C-4') and 162.1 (C-2'). A similar upfield shift of signal due to H-8" at  $\delta$  7.52 in the acetate derivative compared to **3** ( $\delta$  8.54) coupled with  $^1\text{H}-^1\text{H}$  COSY spectrum (Fig. 1) provided confirmation for the structure **3**. However, with the present data it is not possible to assign *E* or *Z*-stereochemistry to the ethylidene part of the molecule.

High resolution NMR spectra were run on a Bruker WM 400 supercon FT NMR spectrometer equipped with ASPECT-2000 computer using TMS as internal reference. The 2D COSY experiment was carried out using N-type phase cycling and a  $90^\circ$  mixing pulse.

Free induction decays were acquired over 1024 data points and 800 Hz for each 256 values of evolution time. The second dimension ( $F_1$ ) sweep width ( $\text{SW}_1$ ) was 400 Hz. The raw data were zero filled in both the dimensions before feeding to double FT using DISNMR programme version 850101.0. The BB and DEPT CMR spectra were obtained at 100.57 MHz using 0.1 *M* solution in 5 mm tube.

The physical data of **3** are as follows; m.p. 243-44° (MeOH); UV(MeOH): 300 (w), 310 (w), 279,

270 (m) and 218 (s) nm; IR(KBr): 1710 and 1670  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$  + one drop TFA): 13.70 (s, OH), 8.64 (m, 10'-H), 8.54 (d,  $J=8.0$  Hz, 8"-H), 7.94 (d,  $J=8.0$  Hz, 7'-H), 7.81 (d,  $J=9.0$  Hz, 5'-H), 7.76 (m, 5"-H), 7.73 (m, 8'-H), 7.71 (m, 6'-H), 7.69 (m, 9'-H), 7.67 (m, 6"-H), 7.58 (dd,  $J=\text{both } 7.0$  Hz, 7"-H), 7.40 (d,  $J=9.0$  Hz, 3"-H), 7.22 (d,  $J=9.0$  Hz, 4"-H) and 2.49 (s, 3H, 1- $\text{CH}_3$ ); CMR: quaternary carbons at  $\delta$  197.6, 164.9, 162.1, 154.7, 150.4, 138.4, 135.6, 122.6, 116.00, 115.1, 113.5 and 113.1, CH carbons at  $\delta$  131.6, 130.0, 128.1, 127.9, 127.6, 126.5, 126.0, 125.0, 124.2, 122.5, 120.0 and 119.8 and  $\text{CH}_3$  carbon at  $\delta$  16.9; MS:  $m/z$  380 ( $\text{M}^+$ ), 365 ( $\text{M}^+ - 15$ , 100%), 237 ( $\text{M}^+ - \alpha\text{-naphthol}$ ), 210, 170 (RDA) and 190 ( $\text{M}^{++}$ ).

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## Synthesis of (*Z*)-11-Hexadecen-1-yl Acetate & Its (*E*)-Isomer

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Synthesis of (*Z*)-11-hexadecen-1-yl acetate(I) and the corresponding *E*-isomer(II) is described. The stereochemistry of the products could be fixed by selective reduction of the common intermediate hept-2-yn-1-ol(III); hydrogenation over Lindlar's catalyst for the sequence of reactions towards I and LAH reduction for the sequence of reactions towards II.

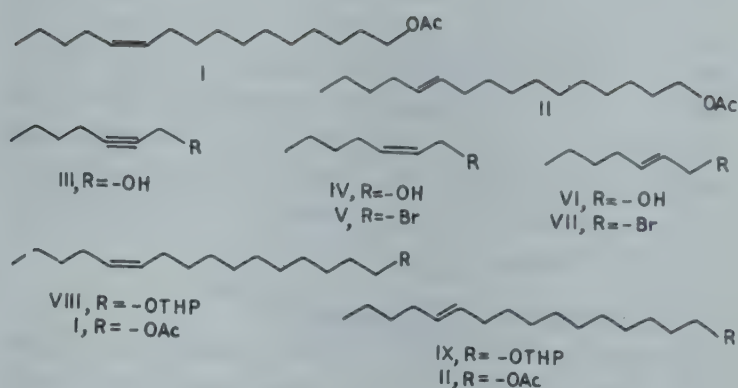
(*Z*)-11-Hexadecen-1-yl acetate(I) is a sex pheromone of the purple stem borer *Sesamia inferenes*<sup>1-2</sup>, a noctuid moth whose larvae attack a wide range of graminaceous crops while (*E*)-11-hexadecen-1-yl acetate (II) is another bioactive component of sex pheromone of female sweet potato leaf folder moth, *Brachmia macroscopa*<sup>3</sup>. We report herein the synthesis of I and II.

The key step in synthesis of I was the coupling of the bromide (V) with the Grignard reagent prepared from 9-bromo-1-tetrahydropyranyloxynonane. These intermediates were prepared as follows:

The dianion of propargyl alcohol on alkylation<sup>4</sup> with 1-bromobutane using lithium metal in liquid NH<sub>3</sub> in the presence of catalytic amount of Fe(NO<sub>3</sub>)<sub>3</sub> provided the acetylenic alcohol(III). The acetylenic bond in III was hydrogenated in the presence of Lindlar's catalyst<sup>5</sup> to get the alcohol(IV) which on bromination (PBr<sub>3</sub>/Py in dry ether) yielded<sup>6</sup> bromide (V).

The OH function in 9-bromononan-1-ol<sup>7</sup> was protected<sup>8</sup> as tetrahydropyranyl ether. The Grignard reagent from this bromide was coupled<sup>9</sup> with bromide (V) under an inert atmosphere at -10 to -5° using catalytic amount of Li<sub>2</sub>CuCl<sub>4</sub> and THF as a solvent to afford VIII. The pyranyl moiety of VIII was removed by refluxing it with MeOH/PTS to furnish the corresponding alcohol which was treated with acetic anhydride<sup>10</sup> and pyridine to yield the corresponding acetate(I). The identity of I was confirmed by its spectral data.

(*E*)-2-Hepten-1-ol (VI), prepared by LAH reduction of acetylenic alcohol (III) in 77% yield, was transformed into the acetate (II) through a reaction sequence parallel to that employed for getting I from IV and its identity was established by its spectral and analytical data.



### Hept-2(*Z*)-en-1-ol(IV)

Hept-2-yn-1-ol (III, 4 g)<sup>4</sup> containing Lindlar's catalyst (0.2 g) and quinoline (1-2 drops) in dry *n*-hexane was stirred under H<sub>2</sub> atmosphere. After one equivalent of hydrogen was taken up, the catalyst was filtered off, the filtrate washed with dil acetic acid, water, dried and solvent removed. The residue chromatographed over silica gel to get TLC pure IV (3.6 g, 90%); IR: 3400, 2950, 2865, 1035 and 730 cm<sup>-1</sup> (*cis* double bond); PMR(CCl<sub>4</sub>): δ 0.96 (3H, *t*, -CH<sub>2</sub>-CH<sub>3</sub>), 1.4 (4H, *m*, saturated methylenes), 2.08 (2H, *d*, *J*=6 Hz, allylic methylenes), 4.18 (2H, *d*, *J*=6 Hz, -CH<sub>2</sub>OH), 4.32 (1H, *s*, -CH<sub>2</sub>OH), 5.55 (2H, *m*, olefinic protons) (Found: C, 73.7; H, 12.4. C<sub>7</sub>H<sub>14</sub>O requires C, 73.6; H, 12.4%).

### 1-Bromo-hept-2(*Z*)-ene(V)

To a solution of IV (3 g) in dry ether (100 ml) containing a few drops of dry pyridine was added slowly with stirring PBr<sub>3</sub> (1.3 ml). Stirring was continued for 2 hr more and reaction mixture refluxed for 2.5 hr (TLC monitoring). The reaction mixture was cooled and poured into ice-water, the organic layer separated and the aqueous layer extracted with ether. The combined organic extract was washed with aq. NaHCO<sub>3</sub> (5%), water, dried and the solvent removed to afford the crude bromide which was used as such in the next step.

### 16-Tetrahydropyranyloxyhexadec-5(*Z*)-ene(VIII)

The Grignard reagent was prepared from dry Mg turnings (0.6 g) and 9-bromo-1-tetrahydropyranyloxynonane (7.6 g) in anhydrous THF (80 ml) under N<sub>2</sub> atmosphere. The contents were stirred and cooled to -10° and to this was added the bromide (V, 4.4 g) in anhydrous THF (30 ml). After stirring for 30 min a catalytic amount of Li<sub>2</sub>CuCl<sub>4</sub> (2 ml) in THF (0.085 g LiCl; 0.135 g CuCl<sub>2</sub> in dry THF) was added. The reaction mixture was stirred further for 4 hr at the same temperature and then left overnight. The reaction was quenched by the addition of a saturated solution of NH<sub>4</sub>Cl, extracted with ether, the organic extract washed with water and dried.

Removal of solvent followed by chromatography of the residue over silica gel afforded pure VIII (3.5 g, 50%); IR: 2930, 2860, 1660, 1460, 1350, 1300, 1200, 1060, 1030, 920, 905, 860, 810 and 750  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ):  $\delta$  0.72 (3H, *t*,  $-\text{CH}_2-\text{CH}_3$ ), 1.00-1.7 (30H, *m*, saturated methylenes and allylic methylenes), 3.1-3.84 (4H, *m*,  $\text{CH}_2-\text{O}-\text{THP}$  and 6- $\text{H}_2$  of THP), 4.45 (1H, *s*, H-2 of THP), 4.75-5.9 (2H, *m*, olefinic protons) (Found: C, 77.3; H, 12.7.  $\text{C}_{21}\text{H}_{40}\text{O}_2$  requires C, 77.7; H, 12.4%).

(*Z*)-11-Hexadecen-1-yl acetate (I)

Compound (VIII, 0.7 g) was stirred at 35-40° with acetyl chloride (0.35 g) and glacial acetic acid (3.5 ml), left overnight, poured onto crushed ice and extracted with ether. The ether extract was washed with aq. sodium bicarbonate (5%) and water, dried and solvent removed. The crude product on purification by column chromatography over silica gel using pet. ether-ether (80:20) afforded I (TLC, single spot); yield 0.5 g (68%); IR: 2900, 2820, 1730, 1625, 1440, 1365, 1230, 1020, 750  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ):  $\delta$  0.9 (3H, *t*,  $-\text{CH}_2-\text{CH}_3$ ), 1.32 (20H, *s*, saturated methylenes), 1.7 (3H, *s*,  $-\text{CO}-\text{CH}_3$ ), 2.0 (4H, *m*, allylic methylenes), 4.02 (2H, *t*,  $-\text{CH}_2-\text{O}-$ ), 4.9-5.7 (2H, *m*, olefinic protons) (Found: C, 76.8; H, 12.0. Calc. for  $\text{C}_{18}\text{H}_{34}\text{O}_2$ : C, 76.6; H, 12.1%).

Hept-2(*E*)-en-1-ol (VI)

To a cooled suspension of LAH (2.5 g) in dry ether (100 ml) was added dropwise, with constant stirring, the acetylenic alcohol (III, 5.9 g) in dry ether (20 ml). The reaction mixture was left overnight at room temperature, and refluxed for 6 hr, cooled and decomposed with a saturated solution of sodium potassium tartrate. The ethereal layer was decanted and the aqueous layer further extracted with ether. The combined organic extract was dried, solvent removed and the residue purified by chromatography over silica gel. Elution with pet. ether-ether (4:1) yielded VI (3.9 g, 77%); IR: 3420-3260, 2930, 2860, 1670, 1460, 1375, 1090, 1010, 965 (*trans* olefin) and 785  $\text{cm}^{-1}$ ; PMR( $\text{CCl}_4$ ):  $\delta$  0.99 (3H, *t*,  $-\text{CH}_2-\text{CH}_3$ ), 1.42 (4H, *m*, saturated methylenes), 2.08 (2H, *m*, allylic methylene), 4.2 (2H, *m*,  $-\text{CH}_2\text{OH}$ ), 5.55 (2H, *m*, olefinic protons) (Found: C, 73.6; H, 12.4.  $\text{C}_7\text{H}_{14}\text{O}$  requires C, 73.6; H, 12.4%).

1-Bromo-2-(*E*)-heptene (VII)

To a well cooled and stirred solution of VI (4.56 g) in dry ether (125 ml) containing a small amount of pyridine, was added  $\text{PBr}_3$  (2 ml) in ether (5 ml) during 15 min. The reaction mixture was left overnight and then refluxed for 1 hr. It was worked-up as described for V. Solvent removal gave the bromide (VII, 5.5 g, 70%); IR: 2960-2850, 1650, 1460,

1390, 1125, 1065, 970 (*trans*-double bond) and 820  $\text{cm}^{-1}$ ; PMR( $\text{CCl}_4$ ):  $\delta$  0.87 (3H, *t*,  $J=6$  Hz,  $-\text{CH}_2-\text{CH}_3$ ), 1.02-1.56 (4H, *m*, saturated methylenes), 2.1 (2H, *m*, allylic methylene), 4.10 (2H, *d*,  $J=6$  Hz,  $-\text{CH}_2\text{Br}$ ), 5.32-5.60 (2H, *m*, olefinic protons).

16-Tetrahydropyranyloxyhexadec-5(*E*)-ene (IX)

The Grignard reagent prepared from dry magnesium turnings (0.6 g) and 9-bromo-1-tetrahydropyranyloxynonane (7.6 g) in anhydrous THF (80 ml) under  $\text{N}_2$  atmosphere was cooled to  $-10^\circ\text{C}$  and to this was added VII (4.4 g). After stirring for 30 min, a catalytic amount of  $\text{Li}_2\text{CuCl}_4$  (2 ml in THF) was added, and the reaction mixture stirred for 4 hr at the same temperature and then left overnight. The reaction mixture was quenched and worked-up as described for VIII. The solvent was evaporated and residue was purified by chromatography over alumina. Elution with pet. ether afforded pure IX (3.7 g, 52%); IR: 2960-2850, 1650, 1470, 1220, 1125, 1060, 1040, 970, 920 and 820  $\text{cm}^{-1}$ ; PMR( $\text{CCl}_4$ ):  $\delta$  0.90 (3H, *t*,  $-\text{CH}_2-\text{CH}_3$ ), 1.32 (26H, *s*, saturated methylenes), 2.0 (4H, *m*, allylic methylenes), 3.35-3.92 (4H, *br*, *m*,  $-\text{CH}_2-\text{O}-\text{CH}-\text{O}-\text{CH}_2-$ ), 4.52 (1H, *s*,  $-\text{O}-\text{CH}-\text{O}$ ), 5.3-5.85 (2H, *m*, olefinic protons) (Found: C, 77.4; H, 12.6.  $\text{C}_{21}\text{H}_{40}\text{O}_2$  requires C, 77.7; H, 12.4%).

(*E*)-11-Hexadecen-1-yl acetate (II)

Compound (IX, 0.7 g) was stirred at 35-40° with acetyl chloride (0.35 g) and glacial acetic acid (3.5 ml), left overnight, poured onto crushed ice and extracted with ether and worked-up as described for the acetate(I). Solvent removal and purification of crude product by chromatography over alumina using pet. ether eluant gave II (0.5 g, 68%) (TLC single spot); IR: 2960-2850, 1725, 1650, 1470, 1250, 1060, 970 (*trans*-double bond) and 920  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ):  $\delta$  0.80 (3H, *t*, saturated methyl), 1.32 (20H, *br*, *s*, saturated methylenes), 1.96 (7H, *m*,  $-\text{C}-\text{CH}_3$  and allylic methylenes), 3.99 (2H, *t*,  $-\text{CH}_2-\text{O}-\text{C}-$ ), 4.9-5.5 (2H, *m*,  $-\text{CH}=\text{CH}-$ ) (Found: C, 76.7; H, 12.0. Calc. for  $\text{C}_{18}\text{H}_{34}\text{O}_2$ : C, 76.6; H, 12.1%).

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## *ortho*-Formylation of a Tyrosine Derivative Using Duff's Reaction

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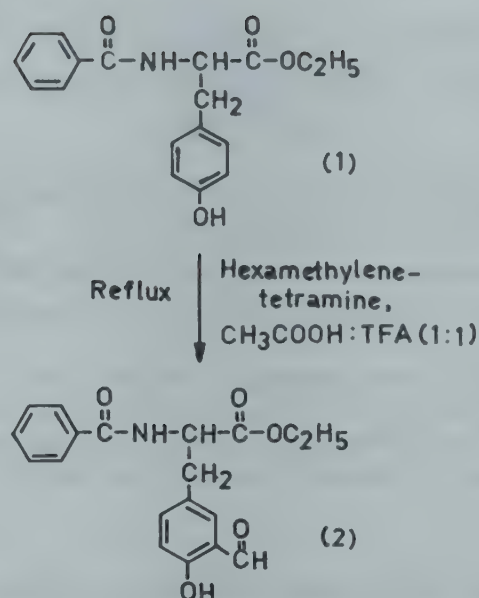
A one-step convenient method for introducing formyl group in *ortho*-position to tyrosine hydroxyl is reported.

For designing antagonist analogues of bradykinin we required 3-formyl-L-tyrosine to be incorporated in the sequence of this peptide hormone. A search through literature revealed to our surprise that 3-formyl-L-tyrosine or its derivatives had not been reported except for a Japanese patent report<sup>1</sup>. These workers introduced a formyl group in 3-position of tyrosine by the oxidation of a primary alcoholic group already present in this position. However, the yield of the desired compound was poor and the source of the starting alcohol derivative of tyrosine was not disclosed.

Duff's<sup>2-4</sup> reaction has been used for introducing formyl groups in phenolic compounds. In this note we wish to report Duff's reaction on a tyrosine derivative (1) which effected the introduction of a formyl group in *ortho*-position to the phenolic hydroxyl of tyrosine. Different acid conditions were used, but the best results were obtained when the reaction was performed in a mixture of anhyd. trifluoroacetic acid and gl. acetic acid. The desired product (2) was readily isolated by column chromatography and characterised by elemental analysis, PMR data and the preparation of its 2,4-dinitrophenylhydrazone derivative. Thus, Duff's reaction allows one to obtain 3-formyl and hence 3-carboxyl derivatives of L-tyrosine which could have interesting analgesic properties.

### Procedure

A solution of N-benzoyl-L-tyrosine ethyl ester (500 mg, 1.5 mmol) and hexamethylenetetramine (900 mg, 6.5 mmol) in 20 ml of anhyd. trifluoroacetic acid-gl. acetic acid (1:1) was gently refluxed for 5 hr, cooled and poured into crushed ice. The separated oily mass was washed several times with cold water, dried and chromatographed on



silica gel column (2.5 × 30 cm) using chloroform-pet. ether (1:1) as eluant. Fractions responding positively to DNP test were pooled and evaporated to give the desired compound (2) as colourless crystals (120 mg) in 30% yield, m.p. 117-118°; *R<sub>f</sub>* 0.56 in CHCl<sub>3</sub>-CH<sub>3</sub>OH (9:1) and 0.66 in *n*-BuOH-AcOH-H<sub>2</sub>O (4:1:1) (Found: C, 66.4; H, 5.6; N, 4.0. C<sub>19</sub>H<sub>19</sub>O<sub>5</sub>N requires C, 66.6; H, 5.6; N, 4.1%); IR(KBr) 3400-3200, 2850, 1740, 1660 and 1250 cm<sup>-1</sup>; PMR(CDCl<sub>3</sub>): δ 1.29 (*t*, 3H, COOCH<sub>2</sub>-CH<sub>3</sub>), 3.31 (*t*, 2H, β-CH<sub>2</sub>-Tyr), 4.22 (*q*, 2H, COOCH<sub>2</sub>CH<sub>3</sub>), 5.06 (*m*, 1H, α-CH); 6.8-7.4 (*m*, 3H, Tyr Ar-H), 7.6 (complex *m*, 5H, Ar-H), 7.8 (*d*, *J* = 7 Hz, 1H, NH), 9.8 (*s*, 1H, formyl proton).

The 2,4-DNP derivative of 2 was obtained readily as orange needles, m.p. 165-66° (Found: C, 57.5; H, 4.4; N, 13.4. C<sub>25</sub>H<sub>23</sub>O<sub>8</sub>N<sub>5</sub> requires C, 57.6; H, 4.4; N, 13.4%).

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## Aliphatic Nitro Compounds: Part II†— Synthesis of 2,6,10,14-Tetramethylpentadec- 2-en-8-one‡

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2,6,10,14-Tetramethylpentadec-2-en-8-one (VIII) is synthesised from 8-nitro-2,6,10,14-tetramethylpentadec-2-ene (VII) which in turn is obtained from 2-chloro-6-methylhept-5-ene, lithium and 4,8-dimethyl-2-nitronon-1-ene using ultrasonic technique.

In a broad programme to develop economical and cheaper methods of synthesis of  $C_{19}$ -hydrocarbons, norphytene and its isomer 2,6,10,14-tetramethylpentadec-2-ene as useful synthons for phytol isomers<sup>1</sup> and phytone<sup>2</sup> employing  $C_{10} + C_1 + C_8$  strategy, herein we report the synthesis of 8-nitro-2,6,10,14-tetramethylpentadec-2-ene (VII) and its conversion into the title compound (VIII) using the nitro group as masked carbonyl. We recently reported the synthesis of vitamin E using these phytol isomers obtained from norphytene by Prins reaction<sup>1</sup>. Recently we also reported<sup>3</sup> the synthesis of 7-nitro-2,6,10,14-tetramethylpentadec-2-ene which was converted into 2,6,10,14-tetramethylpentadec-2-en-7-one (and hence to the corresponding  $C_{19}$ -hydrocarbon) where the nitro group was used as a masked carbonyl.

Our preliminary attempts to prepare VII from 2-chloro-6-methylheptane, the multiple coupling agent 2'-nitro-2'-propane-1'-yl-2,2-dimethylpropanoate (NPP, II)<sup>4</sup> and lithium p,p'-di-*t*-butylbiphenylide (LDBBP) to give the required nitro-olefin (III) failed ( $C_8 + C_3 + C_8$  strategy) (Chart 1). Hence the nitro-olefin (III) was prepared from the corresponding  $C_{10}$ -nitro compound, 3,7-dimethyl-1-nitrooctane (IV) and formaldehyde. Thus dihydrocitronyllyl bromide was treated with sodium nitrite in dimethyl sulphoxide as per literature method<sup>5</sup> to obtain IV in 66% yield; b.p. 100-102°C/15 min; MS:  $m/z$  187 ( $M^+$ ); IR (liquid film): 1550 ( $NO_2$ )  $cm^{-1}$ ; PMR ( $CCl_4$ ): 0.88 (*d*, 9H,  $3CH_3-CH$ ,  $J=6$ Hz), 4.33 (*t*, 2H,  $-CH_2NO_2$ ,  $J\sim 7$  Hz). The nitro compound (IV) was treated with molar

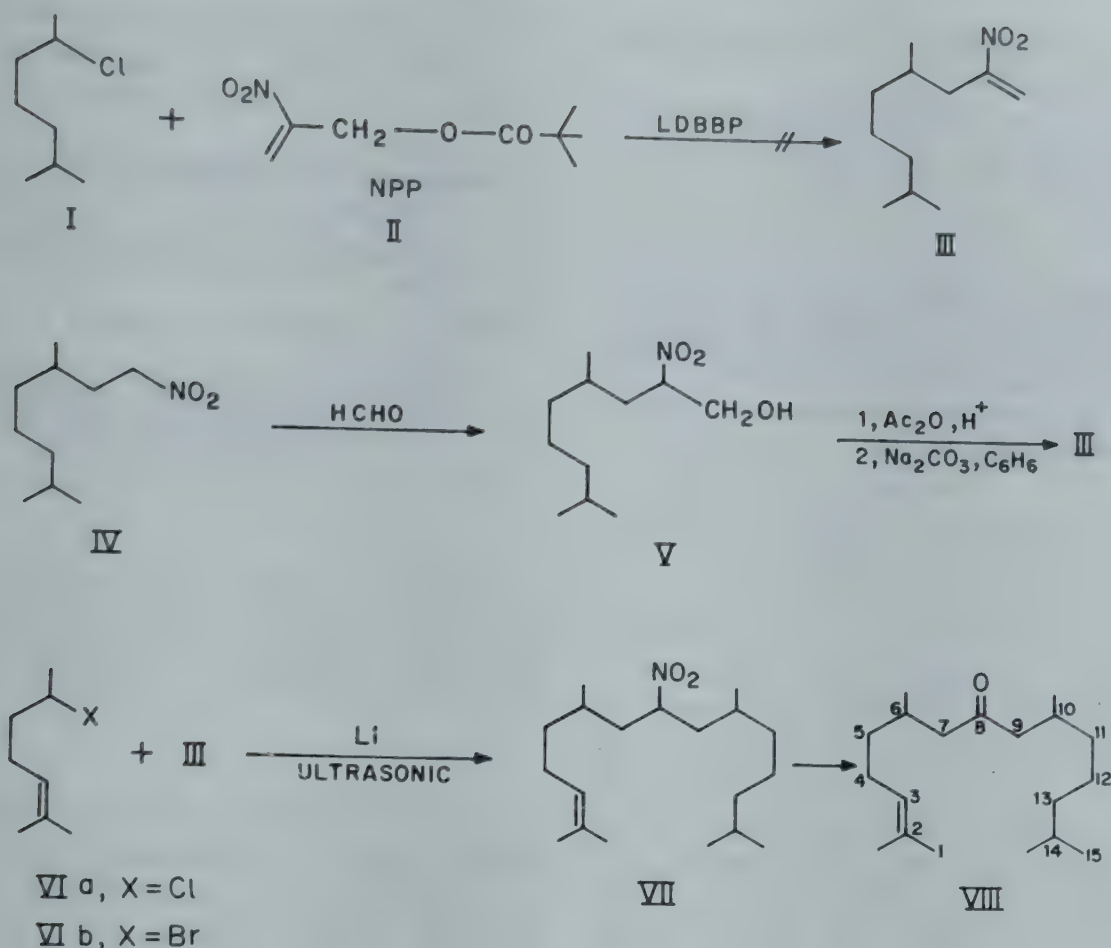
equivalent of paraformaldehyde in methanol using sodium methoxide as the base and stirred for 15 hr. The reaction mixture was poured into water, acidified with dil hydrochloric acid and extracted with ether. The organic layer was washed with 10% aq sodium carbonate, water and dried ( $Na_2SO_4$ ). Evaporation of the solvent gave a residue which showed two spots in TLC with benzene as solvent. The residue was chromatographed over silica gel. Elution with pet ether-10% benzene gave the less polar compound which was identified as nitro-olefin (III) as judged by IR and PMR spectra, while elution with benzene gave the more polar nitro alcohol (V) as judged by IR and PMR spectra. Thus, IR (liquid film) of V displayed bands at 3420 ( $-OH$ ) and 1560 ( $-NO_2$ )  $cm^{-1}$ ; PMR ( $CCl_4$ ): 0.9 (*d*,  $3CH_3-CH$ ,  $J\sim 6$ Hz), 3.83 (*m*, 3H,  $-CH_2OH$ , exchangeable with  $D_2O$ ), 4.76 (*m*, 1H,  $-CHNO_2$ ). The nitro alcohol (V) was acetylated ( $Ac_2O/Conc. H_2SO_4$ ) to give the corresponding nitro acetate which was refluxed with sodium carbonate in benzene<sup>6</sup> to furnish III. The overall yield of III was 51.6%; b.p. 93-90°/1 mm; IR (liquid film): 1540  $cm^{-1}$  ( $-NO_2$ ); PMR( $CCl_4$ ): 0.86 and 0.89 (2*d*, 9H,  $3CH_3-CH-$ ,  $J\sim 6$ Hz), 2.48 (2H,  $-CH_2-C-NO_2$ , AB part of ABX system,  $J_{AB}=15$ Hz,  $J_{AX}=J_{BX}=7$ Hz), 5.4 (*bs*, 1H, olefinic proton *trans* to  $NO_2$ ), 6.3 (*bs*, 1H, olefinic proton *cis* to  $NO_2$ ); MS:  $m/z$  199 ( $M^+$ ).

It is known that Grignard reagent and alkyllithium have been added<sup>4</sup> to nitro-olefin at  $-78^\circ C$ . So the Grignard reagent prepared from  $C_8$ -unit, 2-bromo-6-methylhept-5-ene (VIb) was treated with nitro-olefin (III) in THF at  $-78^\circ C$  and stirred for 4 hr and the reaction mixture allowed to come at room temperature. Usual work-up gave the starting III. Similarly alkyllithium reagent, prepared from 2-chloro-6-methylhept-5-ene (VIa), LDBBP<sup>7</sup> and lithium was cooled to  $-78^\circ C$  and to this was added III in THF dropwise at  $-78^\circ C$  and worked-up. Again the nitro-olefin (III) was recovered unchanged.

As the alkyllithium did not add to III at low temperature, it was decided to carry out the addition reaction at room temperature using sonication to accelerate the rate of reaction. Sonication is usually used in reactions involving metals like Zn, Mg, Li, etc. Ultrasound has been used efficiently in Reformatsky<sup>8</sup>, Grignard or reactions involving alkyllithium<sup>9</sup>.

†For Part I see reference 3.

‡NCL communication No. 4195.



## MASS FRAGMENTATION OF VIII

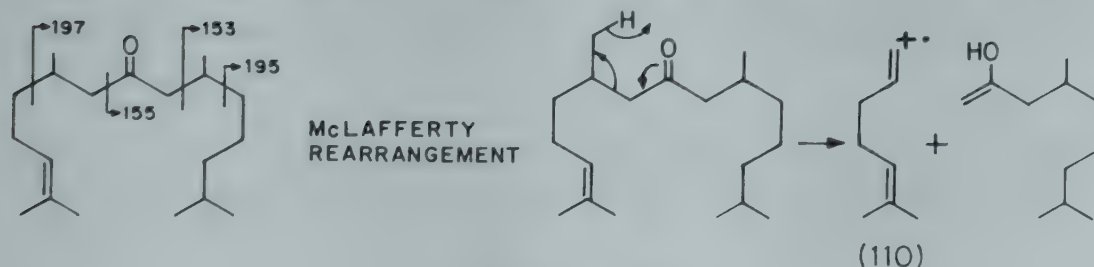


CHART 1

An equimolar mixture of nitro-olefin (III), lithium metal (wire) and 1.2 equivalents of 2-bromo-6-methylhept-5-ene (VIb) was taken in THF. The reaction mixture under nitrogen atmosphere was irradiated in ultrasound laboratory cleaner (220V, 50Hz) till lithium dissolved (45 min). The reaction mixture was poured in 20% aq ammonium chloride and extracted with ether. The ether layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed. The crude product showed in TLC (solvent:pet. ether) the presence of starting VIb, the required VII and a polar compound. The  $\text{C}_{19}$ -nitro compound (VII) was isolated by chromatography over silica gel. The bromo compound (VIb) was obtained in pet. ether eluate while the  $\text{C}_{19}$ -nitro compound (VII) was eluted in petroleum ether containing 15% benzene; yield 40%. No attempt

was made to study other parameters to increase the yield of VII; b.p. 160-62° (bath)/2 mm; IR (liquid film): 1555 ( $-\text{NO}_2$ )  $\text{cm}^{-1}$ ; PMR( $\text{CCl}_4$ ): 0.86 (*d*, 12H,  $4 \times \text{CH}_3-\text{CH}-$ ,  $J \sim 6\text{H}_3$ ), 1.6, 1.67 [2*s*, 6H =  $\text{C}-(\text{CH}_3)_2$ ], 4.68 (*m*, 1H,  $-\text{CHNO}_2$ ), 5.04 (*bt*, 1H,  $=\text{CH}-$ ); MS:  $m/z$  311 ( $\text{M}^+$ ). Compound (VII) was converted into the title compound (VIII) using 15% aq  $\text{TiCl}_3$  as reported earlier<sup>3</sup>; b.p. 150-52° (bath)/2 mm; yield using 76%; single peak in VPC (column OV-101, temp. 180°C); IR (liquid film): 1718 ( $>\text{C}=\text{O}$ )  $\text{cm}^{-1}$ ; PMR( $\text{CDCl}_3$ ): 0.84 (*d*, 12H,  $4 \times \text{CH}_3-\text{CH}-$ ,  $J \sim 6\text{H}_3$ ), 1.56, 1.64 [2*s*, 6H,  $>\text{C}(\text{CH}_3)_2$ ], 5.0 (*bt*, 1H =  $\text{CH}-$ ); MS:  $m/z$  280 ( $\text{M}^+$ ), other fragments at 195, 197, 155, 153 and 110. The ketone (VIII) was identical in all respects with the ketone obtained through enamine route<sup>10</sup>. The reduction of VIII to  $\text{C}_{19}$ -hydrocarbon

2,6,10,14-tetramethylpentadec-2-ene has already been reported by us.

All compounds gave correct elemental analyses.

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## A Novel One-Pot Synthesis of 3-Benzal-2,3-dihydro-4H- 1-benzopyran-4-ones

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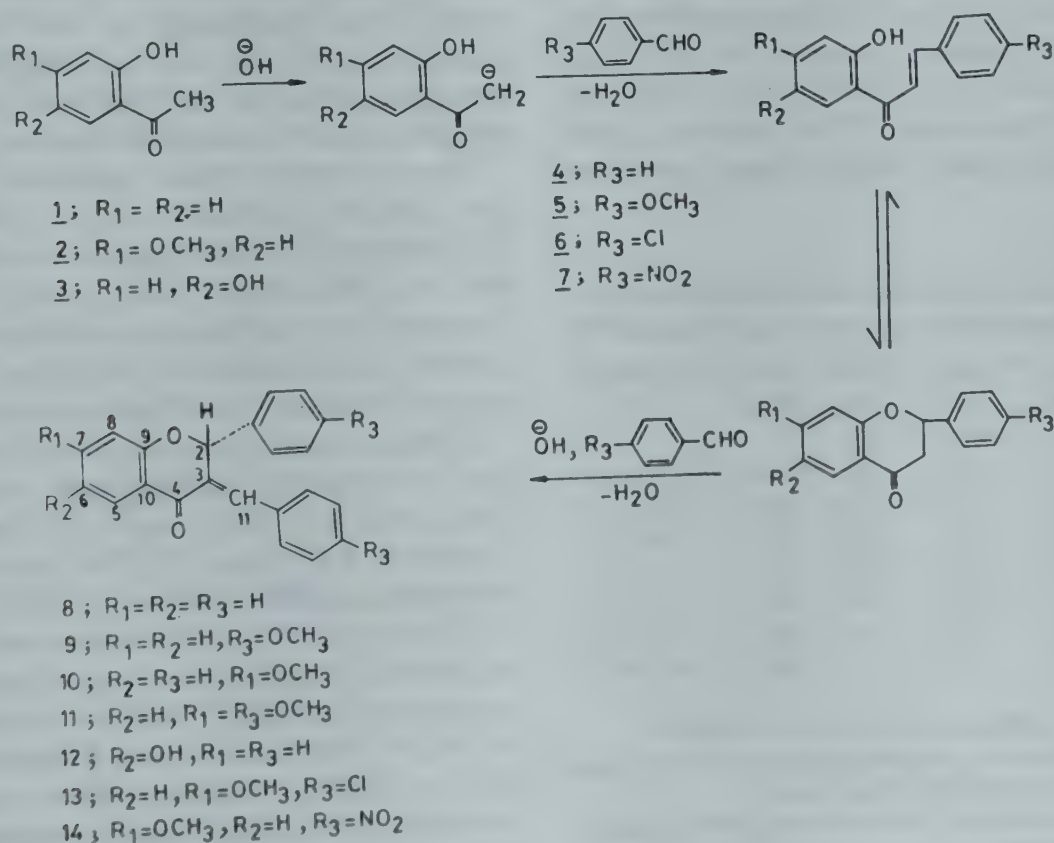
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1987

3-Benzal-2,3-dihydro-4H-1-benzopyran-4-ones (**8-14**) have been synthesized in good yields by a novel one-pot method involving condensation of hydroxyacetophenones with aromatic aldehydes. The reaction is general and has a biogenetic significance.

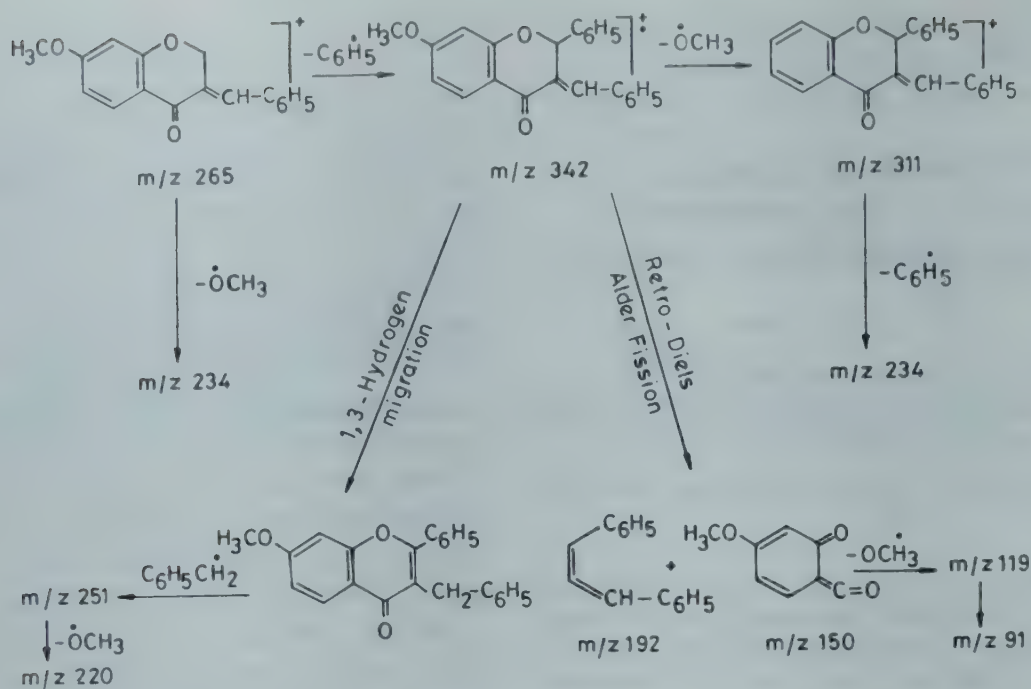
Though chalcones have been synthesized by Claisen-Schmidt condensation of acetophenones and aldehydes using a variety of condensing reagents<sup>1-7</sup>, their yields generally remain moderate which further drop markedly with increasing hydroxylation level of the starting materials. Acyl or ether protection of 2-hydroxyl group of substituted acetophenones and use of crown ethers, though made available some inaccessible chal-

cones, have not been very profitable in improving the yields<sup>8</sup>. We report herein our findings on the reaction which not only revealed the course of the reaction but also offered a novel one-pot procedure for the synthesis of 3-benzal-2,3-dihydro-4H-1-benzopyran-4-ones (**8-14**). These represent an important class of novel compounds which are accessible only by a low-yielding circuitous route<sup>9</sup>.

2-Hydroxyacetophenones (**1-3**) when condensed with aromatic aldehydes (**4-7**) in the presence of aq. alkali yielded the desired benzopyrones (**8-14**; Scheme 1), along with the corresponding chalcones. These products were separated by column chromatography over silica gel. The chalcones were identified by comparison with authentic samples and by their physical and spectral data<sup>10</sup> while the new benzal-2,3-dihydro-4H-1-benzopyran-4-ones were identified on the basis of their elemental analyses and spectral data (IR, PMR, mass). Their IR spectra exhibited a  $\nu_{C=O}$  between 1665 and 1680 and  $\nu_{C=C}$  between 1460 and 1475  $\text{cm}^{-1}$ . Their PMR spectra exhibited the C-2 and C-11 protons consistently at  $\delta$  5.32-5.38 and 6.25-6.37 respectively except for **9** and **14** where the C-11 proton appeared at  $\delta$  6.09 and 6.65 respectively. Other substituent and



SCHEME 1



SCHEME 2

aromatic protons appeared at their expected positions as exemplified in the literature<sup>10</sup>. All these compounds in their mass spectra exhibited an intense fragment resulting from the loss of benzyl group from the molecular ion or its tautomer formed as a result of 1,3-hydrogen migration as depicted in Scheme 2 showing the mass fragmentation of 3-benzal-7-methoxy-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-one (10). The identity of **8** and **12** was further confirmed by preparing their standard samples by acid-catalysed condensation of benzaldehyde with the corresponding flavanones<sup>11</sup>. The reaction conditions and physical data of the products are given in Table 1.

Table 1 – Reaction Conditions and Physical Data of 3-Benzal-2,3-dihydro-4H-1-benzopyran-4-ones (**8–14**)

Reactants*	Reaction period (hr)	Product†	Yield‡ (%)	m.p. °C	Mol. formula
1+4	52	8	38	198	C <sub>22</sub> H <sub>16</sub> O <sub>2</sub>
1+5	72	9	29	168	C <sub>24</sub> H <sub>20</sub> O <sub>4</sub>
2+4	62	10	31	137	C <sub>23</sub> H <sub>18</sub> O <sub>3</sub>
2+5	78	11	17	121	C <sub>25</sub> H <sub>22</sub> O <sub>5</sub>
3+4	58	12	27	211	C <sub>22</sub> H <sub>16</sub> O <sub>3</sub>
2+6	42	13	43	124	C <sub>23</sub> H <sub>16</sub> O <sub>3</sub> Cl <sub>2</sub>
2+7	38	14	51	168	C <sub>23</sub> H <sub>16</sub> N <sub>2</sub> O <sub>7</sub>

\*The alkali used for all these reactions was 10% NaOH.

†All the compounds were characterised by their elemental analyses and spectral data (PMR, IR and mass).

‡The yields are unoptimized and based on consumption of the starting acetophenone.

It was observed that the yield of the benzopyrones increased when the aldehyde component contained an electron withdrawing group. For instance, *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde gave the corresponding benzopyrones (**13** and **14**) in 43% and 51% yields respectively whereas anisaldehyde gave **11** in only 17% yield. These results are in conformity with those expected on the basis of structural considerations. It is interesting to note that Cannizzaro reaction products and conjugate polymers<sup>12</sup>, though expected to be formed under alkaline conditions, are not obtained at all in the reaction.

These results besides providing the first one-pot general synthesis of the novel 3-benzal-2,3-dihydro-4H-1-benzopyran-4-ones, also indicate that the major side products in Claisen-Schmidt hydroxychalcone synthesis are such compounds. The findings are stipulated to have relevance to biogenesis of oxygen heterocycles<sup>13</sup>.

Melting points were determined in open capillaries on an electric melting point apparatus (Adair Dutt) and are uncorrected. IR spectra were recorded in KBr on a SP-1200 grating IR spectrophotometer, PMR spectra in CDCl<sub>3</sub> on a Nicolet-100 MHz Jeol-FT NMR spectrometer using TMS as internal standard and mass spectrum was recorded on an IMS-D 300 Jeol mass spectrometer at 70 eV. The reaction was followed by TLC on silica gel (BDH, Bombay) plates using iodine for visualizing the spots. Organic extracts were usually dried over anhyd. MgSO<sub>4</sub>. Solvents were freshly distilled and purified before use. Solvents were

freshly distilled and purified before use. Pet. ether refers to the fraction having b.p. 60-80°.

### Procedure

In a typical experiment, a solution of 2-hydroxyacetophenone (0.0125 mol) and benzaldehyde (0.0124 mol) in ethanol (15 ml) was added dropwise to an aq. solution of NaOH (10%, 25 ml) and the mixture stirred vigorously with cooling to keep the temperature well below 5°. A distinct colour change was observed and the progress of the reaction monitored by TLC. The reaction mixture was left at room temperature for 38-78 hr, diluted with ice cold water (20 ml) and extracted with ether (3 × 75 ml) to remove unreacted benzaldehyde. The aq. portion was acidified with dil. HCl (0.2 N, 10 ml) to yield an orange yellow solid which on column chromatography over silica gel (100 g) using pet. ether, benzene, chloroform and methanol either alone or in combination as eluants, afforded **8**.

One of the authors (S K S) is grateful to CSIR, New Delhi for the award of a junior research fellowship.

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## Facile Synthesis of Linear & Angular $\alpha$ -Methylfurocoumarins

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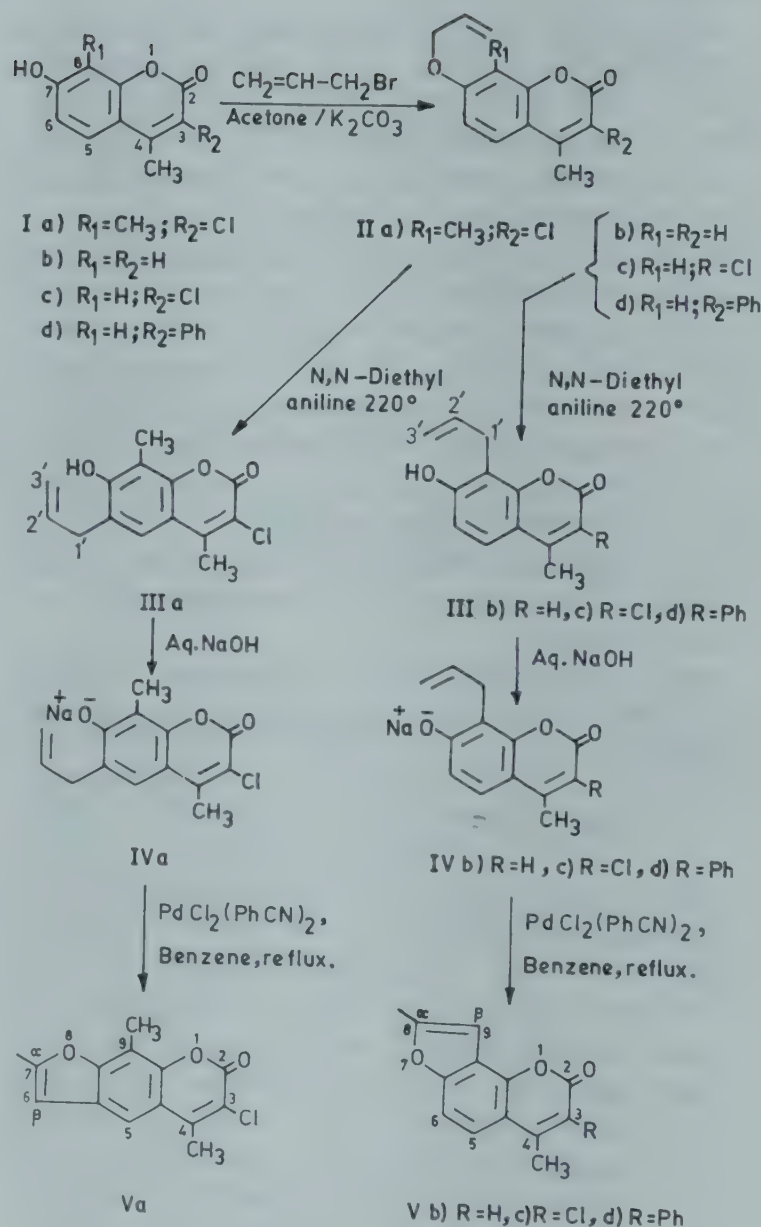
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7-Hydroxy-8/6-allyl-4-methylcoumarins (IIIa-d) on treatment with dil aq. NaOH yield the sodium salts (IVa-d) which when suspended in benzene and treated with dichlorobis(benzonitrile)palladium undergo cyclisation to afford linear (Va) and angular (Vb-d)  $\alpha$ -methylfurocoumarins in 85% overall yield.

$\alpha$ -Methylbenzofurans were obtained quantitatively when 2-allylphenols were subjected to oxidative cyclization with dichlorobis(benzonitrile)palladium<sup>1,2</sup>. In the present investigation this method has been adopted for the synthesis of linear and angular  $\alpha$ -methylfurocoumarins (Va-d).

7-Allyloxycoumarins (IIa-d) were prepared by the allylation of the corresponding 7-hydroxycoumarins<sup>3-6</sup> (Ia-d). Claisen migration of IIa-d in refluxing N,N-diethylaniline (220°) afforded the rearranged products (IIIa-d). These were converted into their corresponding sodium salts (IVa-d). The suspension of the anhydrous sodium salt (IV) in benzene was treated with an equimolar quantity of dichlorobis(benzonitrile)palladium<sup>7</sup> and refluxed for 2 hr. The precipitated metallic palladium was filtered off. The products of the reaction in each case, viz benzonitrile and linear or angular  $\alpha$ -methylfurocoumarins (V) were separated by chromatography over silica gel. The overall yields of Va-d was 85% and there were no traces of the starting IVa-d in the crude reaction product. However, a polymeric substance to the extent of 10-15%, insoluble in common organic solvents, was formed in the reaction. Compared to the several methods available<sup>8-10</sup> for the synthesis of linear or angularly fused  $\alpha$ -methylfurocoumarins, the present method affords a facile route with high overall yields.

The structures of the cyclisation products of IVa-d as linear  $\alpha$ -methylfurocoumarin, 4,7,9-trimethyl-3-chloro-2H-furo[2,3-g][1]benzopyran-2-one (Va) or angular  $\alpha$ -methylfurocoumarins, 4,8-dimethyl-2H-furo[2,3-h][1]benzopyran-2-one (Vb), 4,8-dimethyl-3-chloro-2H-furo[2,3-h][1]benzopyran-2-one (Vc) and 4,8-dimethyl-3-phenyl-2H-furo[2,3-h][1]benzopyran-2-one (Vd) have been established on the basis of spectral data. The IR spectra of Va-d



exhibited the coumarin carbonyl peak at  $1710 \text{ cm}^{-1}$ . In the UV spectra Va-d showed three bands at 220, 250 and 305 nm. In the PMR spectra of Va-d (Table 1), the  $\alpha$ -methyl group appeared as a broad singlet at  $\delta$  2.6 while the furan ring proton appeared as a broad singlet between 6.4 and 6.7. These absorptions are characteristic of protons of  $\alpha$ -methylfuran ring system<sup>2</sup>. In the linear furocoumarin (Va) the  $\text{C}_5\text{-H}$  resonated as a singlet at  $\delta$  7.49 indicating the linear ring fusion. In the angular furocoumarin (Vd), the  $\text{C}_5\text{-H}$  appeared as an AB doublet ( $J = 8.8 \text{ Hz}$ ) at  $\delta$  7.49 while the doublet due to  $\text{C}_6\text{-H}$  merged with other aromatic protons indicating the ring fusion as angular.

The PMR data of Vb and Vc were not helpful in the assignment of angular structure for these, since the signals due to  $\text{C}_5\text{-H}$  and  $\text{C}_6\text{-H}$  merged. Therefore the PMR spectra of the corresponding 8-allyl-

Table 1—Physical and PMR Spectral Data of Linear (Va) and Angular (Vb-d)  $\alpha$ -Methylfurocoumarins

Compd	m.p. (°C)	90 MHz PMR (CDCl <sub>3</sub> ) data, $\delta$ (ppm)
Va	230	2.54 (3H, C <sub>9</sub> -CH <sub>3</sub> ), 2.60 (3H, C <sub>7</sub> -CH <sub>3</sub> ), 2.49 (3H, C <sub>4</sub> -CH <sub>3</sub> ), 7.48 (s, 1H, C <sub>5</sub> -H), 6.40 (1H, C <sub>6</sub> -H)
Vb	183 <sup>9</sup>	2.51 (3H, C <sub>8</sub> -CH <sub>3</sub> ), 2.48 (d, 3H, C <sub>4</sub> -CH <sub>3</sub> ) ( $J=1.0$ Hz), 6.73 (1H, C <sub>9</sub> -H), 7.40 (2H, C <sub>5</sub> -H & C <sub>6</sub> -H), 6.25 (d, 1H, C <sub>3</sub> -H) ( $J=1.0$ Hz)
Vc	253	2.60 (3H, C <sub>8</sub> -CH <sub>3</sub> ), 2.51 (3H, C <sub>4</sub> -CH <sub>3</sub> ), 6.68 (1H, C <sub>9</sub> -H), 7.38 (2H, C <sub>5</sub> -H & C <sub>6</sub> -H)
Vd	144	2.51 (3H, C <sub>8</sub> -CH <sub>3</sub> ), 2.34 (3H, C <sub>4</sub> -CH <sub>3</sub> ), 6.76 (1H, C <sub>9</sub> -H), 7.49 (d, 1H, C <sub>5</sub> -H) ( $J=8.8$ Hz), 7.25-7.47 (m, 6H, C <sub>3</sub> -Ph & C <sub>6</sub> -H)

coumarins (IIIb and IIIc) were studied. In IIIb the C-6 and C-5 protons appeared as *AB* doublets at  $\delta$  6.93 and 7.46 ( $J=8.54$  Hz) while in IIIc these appeared as *AB* doublets at 6.98 and 7.53 ( $J=8.54$  Hz). Thus it is concluded that the Claisen migration of 7-allyloxycoumarins (IIb) and (IIc) furnished 7-hydroxy-8-allylcoumarins (IIIb) and (IIIc) respectively. IIIb and IIIc on cyclisation furnished only angularly fused Vb and Vc respectively. Moreover, it is well established that Claisen migration in 7-allyloxycoumarins, which are unsubstituted at C-8 and C-6, preferentially leads to 7-hydroxy-8-allylcoumarins<sup>11,12</sup>. In the mass spectra of Va-d intense peaks were observed due to the ions  $M^+$ ,  $M-1$  and  $M-CO$ . The  $M-1$  peak is due to the facile loss of a hydrogen from the  $\alpha$ -methyl group followed by rearrangement to give a stable ring-expanded chromenyl ion<sup>13</sup>.

Melting points were determined in a sulphuric acid bath and are uncorrected.

7-Hydroxy-4, 8-dimethyl-3-chlorocoumarin<sup>4</sup> (Ia), 7-hydroxy-4-methylcoumarin<sup>5</sup> (Ib), 7-hydroxy-4-methyl-3-chlorocoumarin<sup>6</sup> (Ic), 7-hydroxy-4-methyl-3-phenylcoumarin<sup>3</sup> (Id), 7-allyloxy-4-methylcoumarin<sup>14</sup> (IIb), 7-allyloxy-4-methyl-3-phenylcoumarin<sup>3</sup> (IIId), and 7-hydroxy-8-allyl-4-methylcoumarin<sup>14</sup> (IIIb) were prepared by reported methods.

7-Allyloxy-4, 8-dimethyl-3-chlorocoumarin (IIa), m.p. 136°, 7-allyloxy-4-methyl-3-chlorocoumarin (IIc), m.p. 89° have now been prepared by refluxing Ia and Ic respectively, with allylbromide in acetone-K<sub>2</sub>CO<sub>3</sub> medium. 7-Hydroxy-6-allyl-4, 8-dimethyl-

3-chlorocoumarin (IIIa), m.p. 158-160°, 7-hydroxy-6-allyl-4-methyl-3-chlorocoumarin (IIIc), m.p. 200-202° and 7-hydroxy-8-allyl-4-methyl-3-phenylcoumarin (IIId), m.p. 242° were prepared by Claisen rearrangement of IIa, IIc and IIId respectively in *N,N*-diethylaniline at 220°.

*General procedure for linear (Va) and angular (Vb-d) furocoumarins by oxidative cyclisation of IVa-d with PdCl<sub>2</sub>(PhCN)<sub>2</sub>*

A suspension of sodium salt (IV, 0.601 mol) in benzene (200 ml) containing PdCl<sub>2</sub>(PhCN)<sub>2</sub> (0.001 mol) was stirred at room temperature for 30 min. The suspension became clear and developed intense red colour during stirring. The clear red solution was refluxed for 2 hr when metallic palladium separated out and the solution turned colourless. Palladium was filtered, the filtrate concentrated and the products in each case ( $\alpha$ -methylfurocoumarin and benzonitrile) were separated by column chromatography on silica gel. Elution with benzene gave benzonitrile and subsequent elution with benzene-ethyl acetate (9:1 v/v) gave the  $\alpha$ -methylfurocoumarins (Va-d) which recrystallized from benzene as colourless prisms. The yields of Va-d are about 85%.

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## Synthesis of Two Naturally Occurring Flavonoids

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The constitutions proposed for isoflavone-D isolated from *Tephrosia maxima* Aers. as 3',4'-dimethoxy-7,8-methylenedioxyisoflavone (I) and of *Pityrogramma triangularis* Var. flavanone as 5-hydroxy-7-methoxy-8-methylflavanone (II) have been confirmed by synthesis.

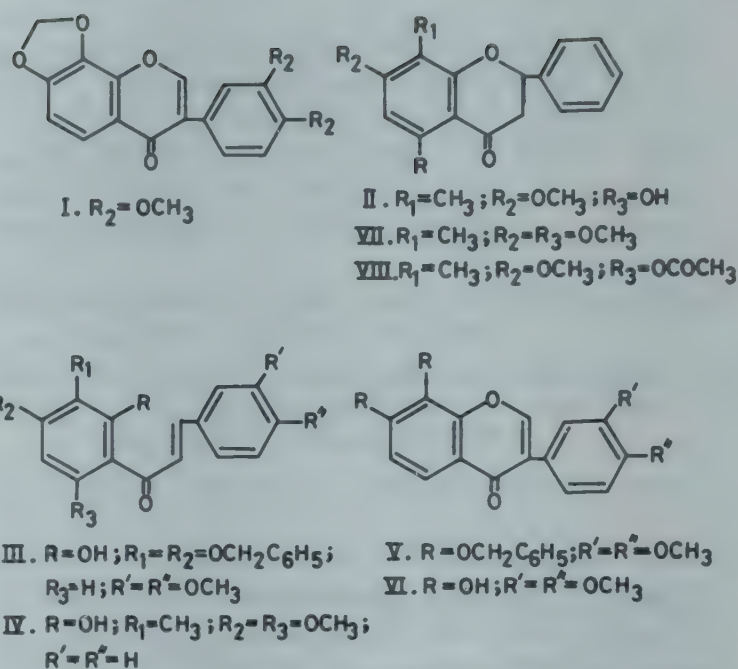
Ward *et al.*<sup>1</sup> isolated an isoflavone D from *Tephrosia maxima* Aers. and designated as maxima isoflavone-D. It was formulated as 3',4'-dimethoxy-7,8-methylenedioxyisoflavone (I) on the basis of spectral data alone. Similarly, Wollenweber *et al.*<sup>2</sup> isolated a flavanone from *Pityrogramma triangularis* Var. and designated it as 5-hydroxy-7-methoxy-8-methylflavanone (II) on the basis of spectral data. Synthetic proof for structures I and II have not been provided as yet. The present note reports the syntheses of I and II.

Compound I was synthesized by oxidative rearrangement of 3',4'-dibenzoyloxy-3,4-dimethoxy-2'-hydroxychalcone (III) with thallium (III) trinitrate<sup>3</sup> followed by debenzoylation and methylenation, whereas II was synthesized by the cyclisation of 2'-hydroxy-3'-methyl-4',6'-dimethoxychalcone (IV) to (VII). Partial demethylation of VII with aluminium chloride in acetonitrile yielded II.

### Synthesis of I

Chalcone (III) was prepared by condensation (room temp., 48 hr) of 3,4-dibenzoyloxy-2-hydroxyacetophenone (1 g) with O-methylvanillin (1.5 g) in the presence of aq. ethanolic KOH (1.5 g in 15 ml water). III was purified as usual and used as such in the next step. It gave a brown colour with ethanolic ferric chloride; PMR(CDCl<sub>3</sub>):  $\delta$  3.92 (6H, s, 2  $\times$  -OCH<sub>3</sub>), 5.36 (4H, s, 2  $\times$  OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 6.88 (1H, s, C<sub>5</sub>-H), 6.92 (1H, s, C<sub>5'</sub>-H), 7.30-7.50 (12H, m, C<sub>6</sub> $\alpha$ -H, C<sub>6</sub> $\beta$ -H and 2  $\times$  OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.62 (2H, s, C<sub>2</sub>-H, and C<sub>6</sub>-H), 7.74 (1H, d, J=10 Hz, C<sub>6</sub>-H).

III (0.36 g) in methanol was treated with Tl(III) nitrate (0.36 g) with stirring at room temperature and the product, 7,8-dibenzoyloxy-3',4'-dimethoxyisoflavone (V) was crystallized from ethyl acetate-pet. ether (0.02 g), m.p. 133-34° (Found: C, 76.0;



H, 5.0. C<sub>31</sub>H<sub>26</sub>O<sub>6</sub> requires C, 75.3; H, 5.2%). It did not give any colour with ethanolic ferric chloride. PMR(CDCl<sub>3</sub>):  $\delta$  3.08 (3H, s, -OCH<sub>3</sub>), 3.16 (3H, s, -OCH<sub>3</sub>), 4.60 (4H, s, -OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.28 (3H, m, C<sub>2'</sub>-H, C<sub>5'</sub>-H and C<sub>6'</sub>-H), 7.32 (10H, m, 2  $\times$  -OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 7.38 (1H, d, J=9 Hz, C<sub>6</sub>-H), 7.54 (1H, d, J=9 Hz, C<sub>5</sub>-H), 7.58 (1H, s, C<sub>2</sub>-H).

V (0.4 g) in acetic anhydride was debenzoylated with Pd/C (0.40 g; 10%) to yield 7,8-dihydroxy-3',4'-dimethoxyisoflavone (VI) (0.2 g), m.p. 145-47°. (Found: C, 64.0; H, 4.8; C<sub>17</sub>H<sub>14</sub>O<sub>6</sub> requires C, 64.9; H, 4.4%). It gave green colour with ethanolic ferric chloride; PMR(CDCl<sub>3</sub>):  $\delta$  3.84 (3H, s, -OCH<sub>3</sub>), 3.92 (3H, s, -OCH<sub>3</sub>), 6.78 (1H, d, J=8 Hz, C<sub>6'</sub>-H), 6.97 (1H, d, J=9 Hz, C<sub>6</sub>-H), 7.04 (1H, dd, J=8 and 2 Hz, C<sub>5'</sub>-H), 7.18 (1H, d, J=2 Hz, C<sub>2'</sub>-H), 7.92 (1H, d, J=8.5 Hz, C<sub>5</sub>-H), 8.06 (1H, s, C<sub>2</sub>-H), 10.54 (2H, s, 2  $\times$  -OH).

Methylenation of VI (0.2 g) with methylene iodide in N,N-dimethylformamide-acetone mixture gave I (0.2 g) m.p. 223-24°. It did not give any colour with ethanolic ferric chloride. (Found: C, 66.0; H, 4.5. Calc. for C<sub>18</sub>H<sub>14</sub>O<sub>6</sub>: C, 66.2; H, 4.3%); PMR(CDCl<sub>3</sub>):  $\delta$  3.92 (3H, s, -OCH<sub>3</sub>), 3.96 (3H, s, -OCH<sub>3</sub>), 6.16 (2H, s, -OCH<sub>2</sub>O-), 6.78 (1H, s, C<sub>6'</sub>-H), 6.97 (1H, d, J=9 Hz, C<sub>6</sub>-H), 7.04 (1H, dd, J=8 Hz and 2 Hz, C<sub>5'</sub>-H), 7.18 (1H, d, J=2 Hz, C<sub>2'</sub>-H), 7.92 (1H, d, J=8.5 Hz, C<sub>5</sub>-H), 8.06 (1H, s, C<sub>2</sub>-H). The m.p. and PMR data of synthetic I agreed with those of the natural sample.

*Synthesis of II*

A solution of 2-hydroxy-4,6-dimethoxy-3-methylacetophenone (1 g) and freshly distilled benzaldehyde (1.5 g) in ethanol (20 ml) was treated with aq potassium hydroxide (3 g in 20 ml) and the reaction mixture was kept at room temperature for 48 hr. Usual work-up afforded the chalcone (IV) which recrystallized from ethyl acetate-pet. ether as yellowish orange needles (1.5 g), m.p. 118-20° (Found: C, 72.4; H, 6.0.  $C_{18}H_{18}O_4$  requires C, 72.4; H, 6.0%). It gave brown colour with ethanolic ferric chloride; PMR( $CDCl_3$ ):  $\delta$  2.08 (3H, s,  $-CH_3$ ), 3.82 (6H, s,  $2 \times -OCH_3$ ), 6.02 (1H, s,  $C_{5'}-H$ ), 7.35 (5H, m,  $C_2-H$ ,  $C_3-H$ ,  $C_4-H$ ,  $C_5-H$  and  $C_6-H$ ), 7.38 (1H, d,  $J=16$  Hz,  $C_\alpha-H$ ), 7.56 (1H, d,  $J=16$  Hz,  $C_\beta-H$ ), 13.32 (1H, s,  $-OH$ ).

A solution of IV (1 g) in alic sulphuric acid (30 ml; 4%) was refluxed for 10 hr. The solution was diluted with water and ethanol distilled under reduced pressure. Usual work-up afforded VII (0.75 g), which was used as such for the next step.

Demethylation of VII (0.2 g) with aluminium chloride (0.5 g) in acetonitrile (60 ml) gave II which crystallized from ethyl acetate-pet. ether as colourless needles (0.15 g), m.p. 230-35° (Found: C, 71.8; H, 5.6. Calc. for  $C_{17}H_{16}O_4$ ; C, 71.8; H, 5.6%). It gave brown colour with ethanolic ferric chloride; PMR( $CDCl_3$ ):  $\delta$  2.0 (3H, s,  $-CH_3$ ), 2.9-3.18 (2H, m,  $C_3-H$ ), 3.75 (3H, s,  $-OCH_3$ ), 5.38 (1H, dd,

$J=11$  and 5 Hz,  $C_2-H$ ), 6.14 (1H, s,  $C_6-H$ ), 7.42 (5H, m,  $C_2'-H$ ,  $C_3'-H$ ,  $C_4'-H$ ,  $C_5'-H$  and  $C_6'-H$ ), 12.12 (1H, s,  $-OH$ ). The m.p. and PMR data of the synthetic II agreed with those of the natural sample. II was also converted into the acetate (VIII) as follows:

Acetylation of II (0.1 g) (Py/ $Ac_2O$ ) in the cold gave VIII which crystallized from chloroform-pet ether as colourless needles (0.08 g), m.p. 104-6° (Found: C, 72.1; H, 5.9.  $C_{19}H_{18}O_5$  requires C, 72.2; H, 5.8%); PMR( $CDCl_3$ ):  $\delta$  1.98 (3H, s,  $-CH_3$ ), 2.20 (3H, s,  $-OCOCH_3$ ), 2.75 (2H, m,  $C_3-H$ ), 3.70 (3H, s,  $-OCH_3$ ), 5.31 (1H, dd,  $J=11$  and 5 Hz,  $C_2-H$ ), 6.42 (1H, s,  $C_6-H$ ), 7.20 (5H, m,  $C_2'-H$ ,  $C_3'-H$ ,  $C_4'-H$ ,  $C_5'-H$  and  $C_6'-H$ ).

My thanks are due to Professor N.R. Banerjee for his valuable guidance and to Head of the Department for providing facilities.

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## Reaction of Flavanones with Chlorosulphonyl Isocyanate

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New heterocyclic systems(I) and (II) have been synthesized by the reaction of flavanones with chlorosulphonyl isocyanate.

Some of our studies on the addition reactions of chlorosulphonyl isocyanate (CSI) have already been reported<sup>1-4</sup>. We report herein the formation of new heterocycles (I and II).

In a typical experiment CSI (0.8 ml; 0.01 mol) was added at room temperature to a solution of flavanone (0.01 mol) in dry dichloromethane (15 ml). The reaction mixture was refluxed for 24 hr, with continuous stirring.

### Isolation of products Ia-d

Petroleum ether was added to the reaction mixture. The red precipitate obtained, was dissolved in acetone-water, acidified with sulphuric acid-water (1:3) and extracted with ether. Evaporation of solvent after drying (Na<sub>2</sub>SO<sub>4</sub>) gave a yellow pasty

mass, which crystallized from benzene-hexane to give light yellow products Ia-d.

### Isolation of IIa-d

From the mother-liquor, solvent was removed and to the residue obtained sodium sulphite was added, followed by acetone (5 ml, 10:1) and allowed to stand for 1 hr. The solution was neutralized (pH=7.5) by careful addition of 5% aq sodium hydroxide and extracted with ether. The ether extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed to give IIa-d.

Structures of Ia-d were arrived at on the basis of IR, PMR and mass spectral data. IR spectra exhibited strong peaks at 1790 and 1680 cm<sup>-1</sup> (>C=O). In the PMR spectra the aromatic protons appeared as a multiplet at  $\delta$  6.8-7.7 and one benzylic proton appeared at 6.2. In addition, the mass spectral data confirmed the assigned structure (Table 1).

Compounds (IIa-d) displayed a strong peak at 1680 cm<sup>-1</sup> due to  $\nu$ C=O and also peaks at 1380 and 1170 cm<sup>-1</sup> characteristic of SO<sub>2</sub> group. In the PMR spectra the aromatic protons appeared as a multiplet in the region  $\delta$  6.8-7.8. The NH proton (flanked by >C=O and SO<sub>2</sub> groups) appeared downfield at  $\delta$  9.2, while the benzylic proton appeared at 6.3 (see Table 1). The assigned struc-

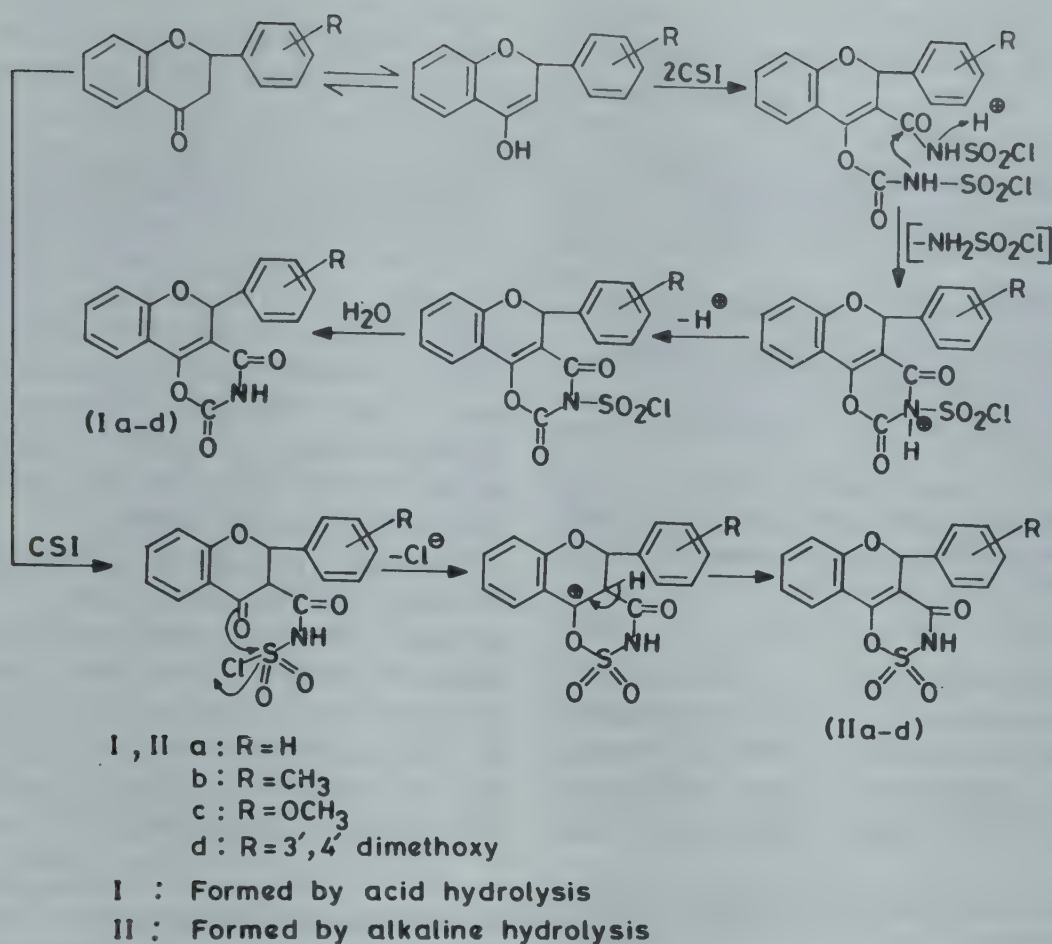
Table 1—Characterization Data of Heterocyclic Compounds (Ia-d) and (IIa-d)

Compd	m.p. <sup>a</sup> (°C)	Yield (%)	Mol. formula <sup>b</sup>	PMR <sup>c</sup>
Ia	183	60	C <sub>17</sub> H <sub>11</sub> NO <sub>4</sub> (293)	6.2 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.8-7.7 (m, 9H, Arom + 1H NH)
Ib	190	58	C <sub>18</sub> H <sub>13</sub> NO <sub>4</sub> (307)	2.4 (s, 3H, CH <sub>3</sub> ), 6.3 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 7.1-7.8 (m, 8H, Arom + 1H NH)
Ic	195	59	C <sub>18</sub> H <sub>13</sub> NO <sub>5</sub> (323)	3.7 (s, 3H, OCH <sub>3</sub> ), 6.2 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 7.0-7.9 (m, 8H, Arom + 1H NH)
Id	187	56	C <sub>19</sub> H <sub>15</sub> NO <sub>6</sub> (353)	3.7 (s, 3H, OCH <sub>3</sub> ), 3.8 (s, 3H, OCH <sub>3</sub> ), 6.4 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.8-7.1 (m, 7H, Arom + 1H NH)
IIa	282	57	C <sub>16</sub> H <sub>11</sub> NO <sub>5</sub> S (329)	6.3 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.9-7.8 (m, 9H, Arom), 9.2 (bs, 1H NH)
IIb	285	61	C <sub>17</sub> H <sub>13</sub> NO <sub>5</sub> S (343)	2.4 (s, 3H, CH <sub>3</sub> ), 6.4 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.8-7.9 (m, 8H, Arom), 9.1 (bs, 1H NH)
IIc	270	63	C <sub>17</sub> H <sub>13</sub> NO <sub>6</sub> S (359)	3.8 (s, 3H, OCH <sub>3</sub> ), 6.4 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.8-7.7 (m, 8H, Arom), 9.3 (bs, 1H NH)
IId	276	66	C <sub>18</sub> H <sub>15</sub> NO <sub>7</sub> S (389)	3.7 (s, 3H, OCH <sub>3</sub> ), 3.8 (s, 3H, OCH <sub>3</sub> ), 6.2 (s, 1H, O-CH-C <sub>6</sub> H <sub>5</sub> ), 6.9-7.7 (m, 7H, Arom), 9.2 (bs, 1H NH)

(a) Melting points were taken on Fisher-Johns melting point apparatus and are uncorrected.

(b) Satisfactory microanalyses were obtained: C  $\pm$  0.35; H  $\pm$  0.25; N  $\pm$  0.30.

(c) PMR spectra of Ia-d were recorded in DMSO-*d*<sub>6</sub> and those of IIa-d in CDCl<sub>3</sub> on a Varian EM-390 (90 MHz) spectrometer; chemical shifts are expressed in  $\delta$ -scale downfield from TMS internal standard.

**Scheme 1**

tures are supported by the mass spectral data. The formation of Ia-d and IIa-d has been rationalized as shown in Scheme 1.

The flavanones were prepared in accordance with the procedure described in the literature<sup>5</sup>.

Authors express their thanks to RSIC, Lucknow for providing facilities for NMR and mass analyses.

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## Synthesis of Substituted Hexahydrofluoren-9-ones

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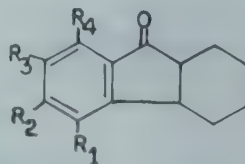
Substituted hexahydrofluoren-9-ones are prepared in one step by the reaction of 1-cyclohexene-1-carboxylic acid with different substituted phenol ethers in the presence of polyphosphoric acid (PPA).

Substituted hydrofluorenones have attracted attention as intermediates for the synthesis of  $\beta$ -norditerpenoids,  $\beta$ -norsteroids<sup>1</sup>, C-nor-D-homosteroids<sup>2</sup> and the gibberellins<sup>3</sup>. These compounds, after expansion of the B-ring<sup>4</sup>, have the potential

of being used for the synthesis of compounds with *cis* A/B ring junction such as the opium alkaloids and some bile acids. However, lack of convenient methods for preparing these compounds has restricted their use in organic synthesis. We describe herein a simple route to synthesise hexahydrofluoren-9-ones in fairly good yields (50 to 60%). The synthetic strategy involves reaction of different phenol ethers with 1-cyclohexene-1-carboxylic acid<sup>5</sup> (I) in the presence of PPA.

Thus, the reaction of 2,3-dimethyl-1-methoxybenzene with the acid (I) led to 7,8-dimethyl-6-methoxy-1,2,3,4,4a,9a-hexahydrofluoren-9-one (**1a**); IR(nujol): 1700  $\text{cm}^{-1}$  ( $>\text{C}=\text{O}$ ); PMR( $\text{CDCl}_3$ ):  $\delta$  0.9-1.85 (8H, *m*,  $\text{CH}_2-1,2,3,4$ ), 2.1 (3H, *s*,  $\text{Ar}-\text{CH}_3$ ), 2.45 (3H, *s*,  $\text{Ar}-\text{CH}_3$ ), 2.6-2.9 (1H, *m*,  $\text{C}_{9a}-\text{H}$ ); 3.0-3.5 (1H, *m*,  $\text{C}_{4a}-\text{H}$ ), 4.0 (3H, *s*,  $-\text{OCH}_3$ ); 6.6 (1H, *s*,  $\text{C}_8-\text{H}$ ).

Table 1—Physical Data of Substituted Hexahydrofluoren-9-ones (**1**)<sup>†</sup>



Compd	Yield %	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Eluting solvent (X:Y)	Crystallisation solvent*	m.p. (°C) b.p. (°C/mm)	Found (%) (Calc.)	
									C	H
<b>1a</b>	60	H	OMe	Me	Me	—	Z	165-67	78.4 (78.7)	8.3 (8.2)
<b>1b</b>	60	H	OEt	Me	Me	—	Z	104-05	79.3 (79.1)	8.1 (8.5)
<b>1c</b>	45	Me	H	Me	OMe	—	—	170-75/3.5	78.4 (78.7)	8.3 (8.2)
<b>1d</b>	40	Me	H	Me	OMe	—	—	140-45/3.5	78.8 (79.1)	8.3 (8.5)
<b>1e</b>	50	Me	H	OMe	Me	10:90	X	87-88	78.3 (78.7)	8.5 (8.2)
<b>1f</b>	45	Me	H	OEt	Me	10:90	X	142-43	78.8 (79.1)	8.3 (8.5)
<b>1g</b>	60	Me	Me	H	OMe	—	Y+X	154-55	78.6 (78.7)	8.4 (8.2)
<b>1h</b>	60	Me	Me	H	OEt	—	Z	143-44	79.3 (79.1)	8.3 (8.5)
<b>1i</b>	55	H	Me	OMe	H	80:20	Y	85-86	78.5 (78.3)	7.5 (7.8)
<b>1j</b>	60	Me	H	OMe	H	50:50	Y	119-20	78.6 (78.3)	7.5 (7.8)
<b>1k</b>	55	OMe	H	H	Me	80:20	Y	129-30	78.2 (78.3)	7.6 (7.8)

\*X = Pet. ether (b.p. 60-80°); Y = benzene; and Z = ethyl alcohol.

†All the above compounds form crystalline 2,4-dinitrophenylhydrazone derivatives and showed the carbonyl bands at 1690  $\text{cm}^{-1}$ .

In a similar manner 2,4-, 2,5-, 3,4-dimethylphenol ethers as well as 2-, 3- and 4-methylphenol ethers reacted with acid (I) to afford compounds (**1c-1k**), whose structures were established on the basis of spectral and analytical data. The PMR data of the compounds followed a similar pattern as that of **1a** with appropriate variation depending on the structure of the product.

For all the hydrofluorenones one could expect them to possess the thermodynamically more stable of the two possible hydrindanone ring junctions. House<sup>6</sup> has shown that for such compounds, the isomer with *cis* fusion is more stable. Our results are in full agreement with these observations. In the PMR spectra the *J* values are found to be 6.6, 6.1 and 8.5 Hz for the 4a-proton and 6.6, 6.8, 6.5 Hz for the 9a-proton. The *J* value of 6.6 which is the same in both the cases corresponds to that for the methine protons, and is less than 8 Hz. Hence the two rings are *cis* fused. Irradiation at 1.33 ppm resulted in the collapse of the multiplet for H-9a into a doublet with *J* around 6.6 Hz, which confirms the *cis*-fusion.

All melting points are uncorrected. The homogeneity of the compounds were ascertained by the TLC on silica gel G-plates.

#### *Reaction of substituted phenol ethers with 1-cyclohexene-1-carboxylic acid (I):*

##### *General procedure*

Phenol ether (0.01 mol) and acid (I) (0.02 mol) were heated in the presence of polyphosphoric acid [prepared from phosphorus pentoxide (10g) and phosphoric acid (5 ml) preheated at 100°C for 0.5 hr]. The reaction mixture was kept at 100°C for further 3 hr with occasional shaking. It was cooled, decomposed with ice water, and left overnight, extracted with chloroform, the chloroform layer washed with saturated aq. NaHCO<sub>3</sub>, water and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was distilled to yield a solid which was either crystallised or chromatographed over neutral alumina.

Various hydrofluoren-9-ones **1a-k** were obtained by the above general procedure in varying yields (Table 1).

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## Intermolecular Dimerization via C – OP Bond Cleavage in Phase Transfer Catalysis Reaction

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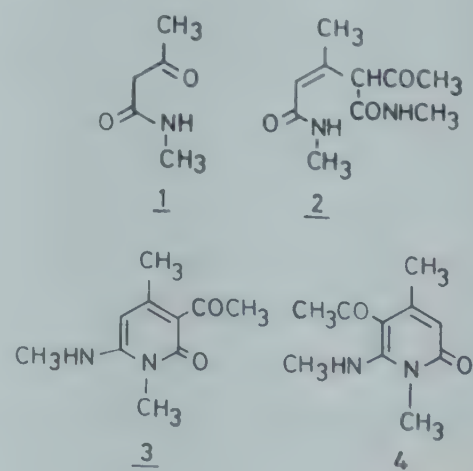
Monomethylacetoacetamide anion under phase transfer condition brings about cleavage of C – OP bond in diethyl phosphorochloridothionate, giving 5-acetyl-6-methylamino-1,4-dimethyl-2-pyridone (**4**) through intermolecular dimerization, besides the enolphosphate (*Z*)-2-butenic acid-3-(diethoxyphosphinothioyl)oxy-N-methylamide.

Reaction of  $\beta$ -dicarbonyl compounds with diethyl phosphorochloridothionate (DPCT) for the synthesis of enolphosphates under phase transfer conditions has been reported recently<sup>1</sup>. During our investigations on similar studies monomethylacetoacetamide (MMAA, **1**) was reacted with DPCT using triethylbenzylammonium chloride as a catalyst along with the cocatalyst triethylenediamine in a two-phase system of aqueous alkali and methylene chloride. The enolphosphate, (*Z*)-2-butenic acid-3-(diethoxyphosphinothioyl)oxy-N-methylamide was isolated along with two additional products. Purification of the reaction mixture on silica gel column, resulted in the elution of the most non-polar compound in the initial fractions. This was identified as tetraethyl dithionopyrophosphate (mol wt 322) known to be a very toxic product<sup>2</sup> (oral  $LD_{50}$  5 mg/kg). This was followed by the enolphosphate mentioned above and the most polar compound formed to an extent of 5%, characterised as a substituted 2-pyridone. This communication describes the mechanism of formation and the structure elucidation of this new pyridone derivative.

Intermolecular condensation of MMAA resulting into cyclic pyridone under thermal and acid catalysed conditions are known earlier<sup>3</sup>. The compound under present study is a solid of, m.p. 172, mol. wt. 194, having an UV absorption at 315 nm in methanol, characteristic of a pyridone system<sup>3</sup>. The IR spectrum in KBr exhibited a broad peak at  $1640\text{ cm}^{-1}$ . The PMR spectrum in  $\text{CDCl}_3$  displayed the 1-N-methyl signal at  $\delta$  3.43 (3H), the NH methyl as a doublet at 2.95, 2.88 and the two C –  $\text{CH}_3$  at 2.67 and 2.32 with the vinyl single

proton signal at 5.66 and a broad NH at 10.67. This downfield chemical shift indicates the intramolecular hydrogen bonding. The  $^{13}\text{C}$ NMR spectrum exhibited the most downfield peak at  $\delta$  201.382 ( $-\text{COCH}_3$ ) followed by the amide carbon at 163.816 with the C-6 and C-4 carbons appearing at 159.112 and 150.305, respectively. The upfield shift of the carbons C-5 and C-3 (101.235 and 93.626) is attributed to the *ortho* and *para* effects due to the aminomethyl substitution at C-6. Similar observations are reported in the substituted pyridines<sup>4</sup>. The four methyl carbons appeared at  $\delta$  32.963, 29.997, 28.769 and 21.549. The C – H coupled spectrum showed the secondary carbon as a doublet centred at 93.626 ( $J = 112\text{ Hz}$ ).

We believe that the structure under discussion has resulted by the nucleophilic attack of MMAA at C-3 of (*Z*)-2-butenic acid-3-(diethylphosphinothioyl)oxy-N-methylamide via the intermediate (**2**). This intermediate can cyclise through the attack of one of the nitrogens on the other amide carbonyl giving either compound **3** or **4**. In a separate experiment MMAA (**1**) under similar condition was found to give less than 0.5% of this new pyridone. The other possible structure, a known compound 1,4,6-trimethyl-5-N-methylcarboxamidopyridine-2-one was ruled out on the basis of the PMR,  $^{13}\text{C}$  and mass spectral data. The resistance of the secondary amino group towards methylation and the carbonyl absorption in IR are indicative of strong intramolecular hydrogen bonding (compound **4**). The loss of  $\alpha$ -fragment ( $-\text{CH}_3$ ) strongly supports the presence of an acetyl group in the molecule. Based on the above data and the mechanistic possibility of its formation, the pyridone has been assigned the structure as 5-acetyl-6-methylamino-1,4-dimethyl-2-pyridone (**4**).



*Representative procedure*

Monomethylacetoacetamide (1.5427 g) in dichloromethane (20 ml) was added with stirring, to a mixture of triethylbenzylammonium chloride (0.067 g), triethylenediamine (0.036 g) and boric acid (0.072 g) in aqueous sodium hydroxide (16%, 5 ml) at room temperature. Diethyl phosphorochloridothioate (2.4 g) was added dropwise to the two-phase system and after the addition was complete the contents were refluxed with stirring for 4 hr. It was cooled, the aqueous layer separated, washed with dichloromethane (10 ml) and the combined organic phase washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude mixture on column chromatography over silica gel using initially a 1:1 mixture of chloroform-ethyl acetate

followed by ethyl acetate afforded the following compounds: Tetraethyldithionophosphate (50%); the enolphosphate (20%) and compound **4** (5%).

We thank Drs M Pardhasaradhi and D S Iyengar for their useful suggestions.

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## Intramolecular Olefinic Cyclisation on Furoic Ester Ring—Scope &amp; Limitations†

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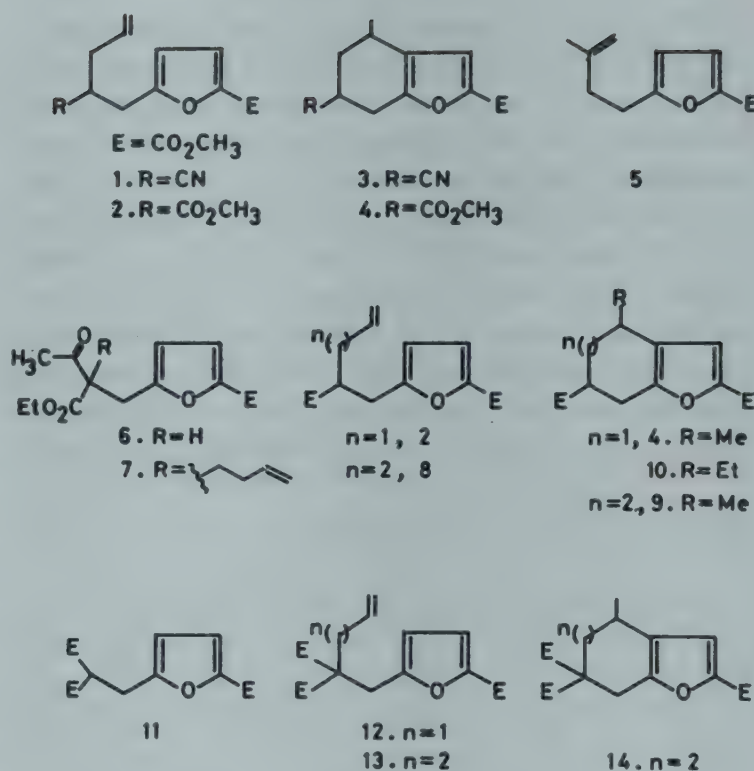
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The scope and limitations of intramolecular Friedel-Crafts cyclisation of terminal olefins on to 2-furoic ester ring system has been investigated in detail. These  $\text{AlCl}_3$ -catalysed cyclisations are unsuitable for 5-membered ring formation. The 6-membered ring formation proceeds in a stereoselective manner only when the 2'-position is tri-substituted; however, the formation of a 7-membered ring is non-stereoselective. These results have been explained on the basis of a mechanism proposed earlier [*Indian J Chem*, **19B** (1980) 320].

We have reported earlier some of our preliminary findings on the intramolecular cyclisation of terminal olefins on to furoic acid ring system<sup>3</sup>. It was observed that the cyclisation of compounds **1** and **2** proceeded smoothly to yield 6-membered ring compounds **3** and **4** respectively. The cyclisation was thus found to be insensitive to the polar group present at 2'-position on the side chain. Furthermore, it was found to proceed well only in the presence of AlCl<sub>3</sub> as Friedel-Crafts catalyst<sup>4</sup>. On the other hand, attempted cyclisation of **5** led only to polymeric products. We report here the results of a detailed study on the scope and limitations of these cyclisation reactions.

As reported earlier, alkylation of **6**<sup>3</sup> with alkyl bromide followed by alkaline hydrolysis and esterification yielded **2**. It was subjected to cyclisation using  $\text{AlCl}_3/\text{CS}_2\text{—CH}_2\text{Cl}_2$  under reflux. The homogeneous product which was obtained after repeated column chromatography in 68% yield analysed for  $\text{C}_{13}\text{H}_{16}\text{O}_5$ . It was found to be a mixture of two isomers of the cyclisation product **4** by PMR data and HPLC, and an isomeric ratio of 1:3 was thus established. In addition, a small amount (5%) of a new uncyclised product was also isolated which was not characterised.

Alkylation of **6** with 4-bromobutene<sup>5</sup> yielded **7** which on alkaline hydrolysis followed by esterification gave **8**. This compound on usual cyclisation and



work-up afforded a homogeneous product (TLC) in 65% yield which analysed for  $C_{14}H_{18}O_5$ . The PMR spectrum however suggested the product to be a mixture of **9** and **10** in 2:1 ratio. But the mixture was inseparable by column chromatography.

Alkylation of **11** with allyl bromide gave **12** in 56% yield. Attempted cyclisation of **12** in  $\text{AlCl}_3/\text{CS}_2-\text{CH}_2\text{Cl}_2$  or  $\text{AlCl}_3/\text{C}_6\text{H}_5\text{NO}_2$  at different temperatures (room temperature to  $150^\circ$ ) remained unsuccessful. The starting material was always recovered unchanged. On the other hand, the olefinic compound **13**, obtained by alkylation of **11** with 4-bromobutene (54% yield), underwent facile cyclisation under usual conditions ( $\text{AlCl}_3/\text{CS}_2-\text{CH}_2\text{Cl}_2$ , reflux) to give **14** in 71% yield. Recently Walsh *et al.*<sup>6</sup>, have also observed that the attempted cyclisation of 3-(2-furyl)propionyl chloride failed to give any 5-membered ring ketone; however, the homologous 6-membered ring ketone could be easily obtained from 4-(2-furyl)butanoyl chloride.

Thus the above observations led to the following conclusions:

- (i) The cyclisation proceeds well only when anhydrous  $\text{AlCl}_3$  is used as Friedel-Crafts catalyst.
- (ii) Attempts to form 5-membered ring system does not succeed.
- (iii) When the 2'-position is tri-substituted 6- as well as 7-membered ring formation proceed well. The 6-membered ring formation is found to be insensitive to polar group present at the 2'-position.

† Part IV of the series "Chemistry of Furans". For Parts I-III see refs 1, 2 and 3 respectively.

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(iv) When the 2'-position is tri-substituted, cyclisation to 6-membered ring products proceeds with a high degree of stereoselectivity; however, 7-membered ring formation is non-stereoselective.

(v) When the 2'-position is tetra-substituted, cyclisation to 6-membered ring does not proceed at all; however 7-membered ring formation proceeds well under normal conditions.

### Mechanism

As suggested earlier<sup>3</sup> these reactions proceed via the formation of a complex involving furano-oxygen,  $\text{AlCl}_3$  and the terminal olefin. When the chain is short (I) the developing carbonium ion would remain far away from the electron rich C-4 position of the furan ring<sup>7</sup>. Therefore, the stereo-electronic requirement for such a cyclisation cannot be attained. When the side chain is longer (II) the carbonium ion can easily orient to the correct position thereby facilitating the cyclisation.

The formation of such a complex in the case of **2** could lead to four distinct conformers (III-VI). Considerations similar to those of bio-genetic type cyclisation reactions, suggest that of the preferred chair type foldings IV and V (as the molecule progresses along the reaction co-ordinate) conformation IV would develop 1, 3-diaxial interaction in the transition state, whereas conformation V would have the developing methyl group on the phase opposite to that of the ester group and therefore has no unfavourable interaction in the transition state. The preferred conformation V thus leads to a greater selectivity dur-

ing 6-membered ring formation. When cyclisation proceeds to form a 7-membered ring (**8**  $\rightarrow$  **9**), the developing methyl group and the ester moiety at the 2'-position would be 1, 4- and therefore no unfavourable interaction would develop during the transition state. Therefore, the 7-membered ring formation is nonstereoselective.

Compound **12** was recovered unchanged even under more drastic conditions because unfavourable 1, 3-diaxial interactions in the transition state would develop in the  $\alpha$ - as well as  $\beta$ -attacks and thus render the reaction difficult to proceed. However, compound **13** does not encounter such unfavourable interactions in the transition state for the reasons discussed above.

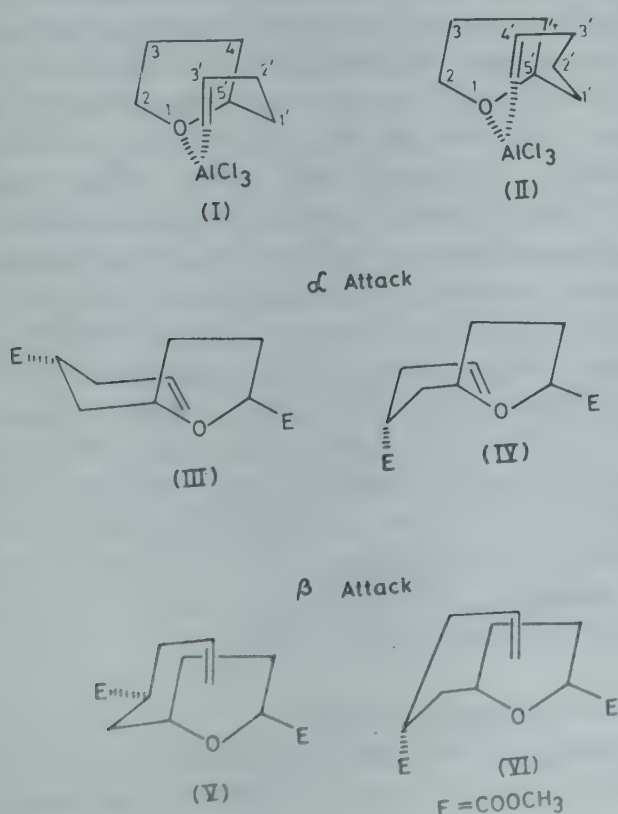
Since direct cyclisation of **8** yielded a mixture of **9** and **10** selective decarboxylation of **14** was attempted. When subjected to  $\text{NaCl/DMSO}$  conditions of Krapcho and Lovey<sup>8</sup>, **14** underwent smooth decarboxylation to yield **9** as a 1:1 mixture of its isomers. The PMR spectrum of the product thus obtained confirmed the assignments made for the complex mixture obtained from **8**.

### Compound 7

To a suspension of  $\text{NaH}$  (0.3 g, 12.5 mmol) in dry DMF (15 ml) was added **6** (1.3 g, 5 mmol) in dry DMF (5 ml) and the mixture stirred under nitrogen atmosphere for 1 hr at room temperature followed by 15 min at  $50^\circ$ . 1-Bromo-3-butene (1 g, 7 mmol) in DMF (5 ml) was then added dropwise to it and the reaction mixture stirred for 12 hr at room temperature, poured into water, extracted with ether ( $5 \times 20$  ml), washed with brine and dried (anhyd  $\text{Na}_2\text{SO}_4$ ). Removal of solvent and distillation of the residue *in vacuo* (bulb-to-bulb,  $146^\circ/0.04$  mm) gave the pale yellow compound **7** (0.676 g) in 42% yield. (Found: C, 63.1; H, 6.8%.  $\text{C}_{17}\text{H}_{22}\text{O}_6$  requires C, 63.3; H, 6.9); IR (film): 1720s (ester and acetyl CO), 1640w (double bond), 1600w (aromatic)  $\text{cm}^{-1}$ ; PMR ( $\text{CCl}_4$ ):  $\delta$  1.3 (*t*, 3H,  $-\text{COOCH}_2\text{CH}_3$ ), 1.93 (*m*, 2H,  $-\text{CH}_2-$ ), 2.15 (*s*, 3H,  $-\text{COCH}_3$ ), 2.44 (*m*, 2H,  $=\text{CH}-\text{CH}_2-$ ), 3.3 (*s*, 2H,  $-\text{CH}_2\text{Ar}$ ), 3.83 (*s*, 3H,  $-\text{COOCH}_3$ ), 4.28 (*q*, 2H,  $-\text{COOCH}_2-\text{CH}_3$ ), 4.82–5.35 (*m*, 2H,  $\text{CH}_2=\text{CH}-$ ), 5.48–6.1 (*m*, 1H,  $\text{CH}_2=\text{CH}-$ ), 6.25 (*d*, 1H,  $\text{C}_4\text{-H}$ ), 7.06 (*d*, 1H,  $\text{C}_3\text{-H}$ ).

### Compound 8

Compound **7** (0.4 g, 1.2 mmol) was added to an aq. ethanolic (2.5 ml each) solution of  $\text{NaOH}$  (0.248 g, 6.2 mmol) and the reaction mixture stirred for 15 hr at room temperature, water (10 ml) added to it and extracted with ether, the aq. layer acidified with ice-cold  $\text{HCl}$ , extracted with ether ( $6 \times 20$  ml), the extract dried (anhyd.  $\text{Na}_2\text{SO}_4$ ) and the solvent removed. The residue thus obtained was esterified with diazome-



thane and distilled *in vacuo* (bulb-to-bulb, 139°/0.04 mm) to give **8** (0.247 g) as a pale yellow liquid, yield 75% (Found: C, 63.4; H, 7.2.  $C_{14}H_{18}O_5$  requires C, 63.2; H, 6.8%); IR (film): 1730s (ester CO), 1640w (double bond), 1600w (aromatic)  $cm^{-1}$ ; PMR ( $CCl_4$ ):  $\delta$ 1.56-2.33 (*m*, 4H, =CH—CH<sub>2</sub>—CH<sub>2</sub>—), 2.9 (*m*, 3H, —CH—CH<sub>2</sub>—Ar), 3.71 (*s*, 3H, —COOCH<sub>3</sub>), 3.88 (*s*, 3H, Ar—COOCH<sub>3</sub>), 5.06 (*m*, 2H, —CH<sub>2</sub>=CH—), 5.47-6.06 (*m*, 1H, CH<sub>2</sub>=CH—), 6.21 (*d*, 1H, C<sub>4</sub>—H), 7.08 (*d*, 1H, C<sub>3</sub>—H).

#### Cyclisation of **8**

To a suspension of anhyd.  $AlCl_3$  (0.6 g, 4.5 mmol) in methylene chloride—carbon disulphide (1:1, 10 ml) at room temperature, compound **8** (0.2 g, 0.75 mmol) in dry methylene chloride (5 ml) was added dropwise with stirring. The reaction mixture was refluxed for 5 hr, cooled to room temperature, and hydrolyzed with dil. ice-cold HCl under cooling. The organic layer was separated and the aq. layer extracted with methylene chloride (5 × 10 ml). The combined organic layer was washed once with dil. HCl, water, 5% aq. sodium bicarbonate and finally with water, dried (anhyd.  $Na_2SO_4$ ), filtered and solvent removed to give a thick residue which on column chromatography over neutral alumina followed by distillation *in vacuo* (bulb-to-bulb, 166-168°/0.04 mm) provided a mixture of **9** and **10** (0.130 g) in 65% yield (Found: C, 63.5; H, 6.8.

$C_{14}H_{18}O_5$  requires C, 63.2; H, 6.8%, IR ( $CHCl_3$ ): 1720s (ester CO), 1620w (aromatic)  $cm^{-1}$ ; PMR ( $CCl_4$ ):  $\delta$ 3.83 (aromatic ester methyl protons), 3.68, 3.70 and 3.75 (aliphatic ester methyl protons).

#### Compound **12**

To a suspension of sodium hydride (0.213 g, 8.88 mmol) (50% in mineral oil, washed with 3 × 8 ml dry pentane) in dry DMF (20 ml), compound **11** (1 g, 3.70 mmol) in dry DMF-benzene (4:1, 5 ml) was added and the mixture stirred under nitrogen atmosphere for 45 min at room temperature followed by 15 min at 50°. Allyl bromide (0.492 g, 4.07 mmol) in dry DMF (5 ml) was added dropwise to the above mixture and stirring continued further for 8 hr at room temperature. The reaction mixture was poured into water (20 ml), extracted with ether-benzene (4:1, 5 × 20 ml), washed with water, brine, dried (anhyd.  $Na_2SO_4$ ) and solvent removed. The residue on column chromatography followed by distillation *in vacuo* (bulb-to-bulb, bp. 145-150°/0.05 mm) gave **12** (0.56 g) in 56% yield (Found: C, 58.2; H, 6.0.  $O_{15}H_{18}O_7$  requires C, 58.1; H, 5.8; IR (film): 1720-1740 (ester CO), 1640w (double bond), 1590w (aromatic)  $cm^{-1}$ ; PMR ( $CCl_4$ ):  $\delta$ 2.56 (*d*, 2H, CH<sub>2</sub>—CH=CH<sub>2</sub>), 3.25 (*s*, 2H, CH<sub>2</sub>—fu), 3.76 (*s*, 3H, aliphatic —COOCH<sub>3</sub>), 3.83 (*s*, 3H, Ar—COOCH<sub>3</sub>), 4.90-5.50 (*m*, 3H, —CH=CH<sub>2</sub>), 6.16 (*d*, 1H, C<sub>4</sub>—H) 7.00 (*d*, 1H, C<sub>3</sub>—H).

#### Compound **13**

To a suspension of sodium hydride (0.213 g, 8.88 mmol) (in 50% mineral oil) in dry DMF (20 ml), Compound **11** (1 g, 3.70 mmol) in dry DMF-benzene (4:1, 10 ml) was added and the mixture stirred under dry nitrogen atmosphere for 45 min at room temperature followed by 15 min at 50°. 1-Bromo-3-butene (0.55 g, 4.07 mmol) in dry DMF (5 ml) was then added dropwise to the above mixture and stirring continued further for 12 hr at room temperature. The reaction mixture was poured into water (20 ml) and extracted with ether-benzene (6 × 20 ml). The combined organic layers were washed with water (15 ml) and brine (15 ml), dried (anhyd.  $Na_2SO_4$ ) and filtered. Removal of solvent under reduced pressure gave a crude product which on purification by column chromatography followed by distillation *in vacuo* (145-150°/0.02 mm) afforded **13** (0.54 g) as a pale yellow oil in 54% yield (Found: C, 59.0; H, 6.0.  $C_{16}H_{20}O_7$  requires C, 59.2; H, 6.2%); IR (film): 1720-1730s (ester CO), 1640w (double bond), 1590w (aromatic)  $cm^{-1}$ ; PMR ( $CCl_4$ ):  $\delta$ 1.88 (*br s*, 4H, =CH—CH<sub>2</sub>—CH<sub>2</sub>—), 3.25 (*s*, 2H, —CH<sub>2</sub>—fu), 3.70 (*s*, 7H, aliphatic 2 × COOCH<sub>3</sub> and CH<sub>2</sub>=CH—), 3.76 (*s*, 3H, Ar—COOCH<sub>3</sub>), 4.75-5.15 (*m*, 2H, —CH=CH<sub>2</sub>), 6.06 (*d*, 1H, C<sub>4</sub>—H), 6.90 (*d*, 1H, C<sub>3</sub>—H).

#### Cyclisation of **14**

To a suspension of anhyd.  $AlCl_3$  (0.658 g, 4.93 mmol) in dry methylene chloride-carbon disulphide (1:1, 25 ml) at room temperature, compound **14** (0.4 g, 1.23 mmol) in dry methylene chloride (10 ml) was added dropwise with stirring. The reaction mixture was refluxed for 5 hr and hydrolysed with dil. ice-cold HCl under cooling. The organic layer was separated and the aq. layer was extracted with methylene chloride (6 × 20 ml). The combined organic layers were washed once with dil. HCl, water 5% aq. sodium bicarbonate and finally with water, dried (anhyd.  $Na_2SO_4$ ) and filtered. Removal of solvent under reduced pressure gave a crude product which on purification by column chromatography afforded pure **14** which recrystallised from pet. ether (40-60°)-ethyl acetate (10:1) as colourless crystals; yield 0.284 g (71%) (Found: C, 59.3; H, 6.0.  $C_{16}H_{20}O_7$  requires C, 59.3; H, 6.2%); IR (KBr): 1730s (ester CO), 1610w (aromatic)  $cm^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$ 1.20 (*d*, 3H, —CH<sub>3</sub>), 1.35-2.77 (*m*, 5H, CH—CH<sub>2</sub>—CH<sub>2</sub>—C—), 3.26 and 3.5 (*AB* pattern, 2H, —CH<sub>2</sub>—Ar), 3.70 (*d*, 6H, aliphatic 2 × COOCH<sub>3</sub>), 3.83 (*s*, 3H, Ar—COOCH<sub>3</sub>), 7.00 (*s*, 1H, C<sub>3</sub>—H).

#### Decarboxylation of **14** to **9**

A mixture of **14** (2.96 g, 10 mmol), NaCl (0.878 g, 15 mmol), water (0.5 ml) and DMSO (15 ml) was heat-

ed at 140-160° for 4 hr, solvent removed under reduced pressure and the residue poured into water (15 ml) and extracted with ether (6 × 20 ml). The combined organic layers were washed with brine, dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>) and filtered. Removal of solvent under reduced pressure followed by distillation of the residue at 140-145°/0.02 mm gave the decarboxylated product **9** (1.59 g) in 60% yield (Found: C, 63.1; H, 6.7. C<sub>14</sub>H<sub>18</sub>O<sub>5</sub> requires C, 63.2; H, 6.8%); IR (film): 1720s (ester CO), 1590w (aromatic) cm<sup>-1</sup>; PMR (CDCl<sub>3</sub>): δ 1.24 (4 lines, 3H, —CH—CH<sub>3</sub>), 1.35-3.26 (*m*, 6H, —CH—CH<sub>2</sub>—CH<sub>2</sub>—CH—), 3.64 (*d*, Ar—CH<sub>2</sub>—), 3.66 (*d*, 3H, aliphatic —COOCH<sub>3</sub>), 3.82 (*s*, 3H, Ar—COOCH<sub>3</sub>), 7.03 (*d*, 1H, C<sub>3</sub>—H).

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## Regioselective Functionalization of Alkyl Aryl Ethers

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A new procedure for regioselective functionalization of sensitive alkyl aryl ethers has been proposed as an alternative to picrate and sulphonamide derivatives. The procedure is based upon their reaction with cerium(IV) ammonium nitrate (CAN) and gives good yields of nitro substituted ethers, affording one pot synthesis of hitherto unknown, 1-isopropoxy-4-nitronaphthalene, 1-butoxy-4-nitronaphthalene, 2-isopropoxy-6-nitronaphthalene and 2-butoxy-6-nitronaphthalene. A plausible mechanism has been suggested.

The chemical derivatization of alkyl aryl ethers for characterization purposes is generally achieved by converting these into picrates and sulphonamides<sup>1,2</sup>. Though picrates and sulphonamides are obtained as easily characterizable solids, they are obtained by multi step processes. The disadvantages are instability of picrates during crystallization and involvement of corrosive and environmentally hazardous chlorosulphonic acid in the preparation of sulphonamides. Sometimes hydrolytic cleavage with HI, bromination and nitration procedures are also helpful to derivatise aromatic ethers but they are of little value when the aromatic rings contain sensitive groups like  $-OH$ ,  $-OCH_3$  and  $-NH_2$ . In bromination and nitration, over oxidation poses a major problem particularly when alkyl aryl ethers contain more than one benzene ring fused together. We present herein a convenient one-pot procedure for derivatisation of alkyl aryl ethers. The procedure involves reaction of cerium(IV) ammonium nitrate (CAN) with alkyl aryl ethers, when solid nitro ethers are obtained in acceptable yields. The methodology adopted also enables one to have hitherto unknown synthetic derivatives of alkoxy-naphthalenes such as 1-isopropoxy-4-nitronaphthalene, 1-butoxy-4-nitronaphthalene, 2-isopropoxy-6-nitronaphthalene and 2-butoxy-6-nitronaphthalene. It is significant to note that the reaction does not lead to oxidation of substrates to naphthaquinones as reported earlier in the reaction<sup>3</sup> using cerium(IV) ammonium sulphate in  $CH_3CN/dil. H_2SO_4$ . Acetoxylation of substrates observed by earlier workers in benzene series of compounds under similar conditions<sup>4,5</sup> is not observed in the present procedure. For a compara-

tive study, we have also carried out the nitration of alkyl aryl ethers with  $HNO_3/H_2SO_4$  but obtained mixtures of products which were difficult to separate. In contrast to this the use of cerium(IV) ammonium nitrate affords a high degree of regioselectivity and in majority of cases only one product is obtained in good yield.

Though the mechanism of the reaction is unclear at the moment, we would like to stress that the reaction does not occur in the presence of cerium(IV) ammonium sulphate + ammonium nitrate and reaction rate is unaffected by addition of alkali metal nitrate indicating that nitronium ions are not involved in the reaction<sup>5</sup>. The intermediacy of a radical cation is also ruled out because the expected formation of corresponding acetates by competitive oxidative solvolysis and formation of nitrates by oxidative displacement was not observed<sup>6</sup>. One probable explanation for the observation is the formation of cerium(IV)-aromatic moiety complex by ejection of nitrate ion from the ligand coordination sphere which remains entrapped in the solvent cage or can remain attached to the substrate by non-covalent forces. The complex can then decompose to yield unstable aryl nitrates leading to the nitro substituted products.

### Preparation of alkyl aryl ethers

Alkoxy-naphthalenes (**1-9**) were synthesized by alkylation of the hydroxynaphthalenes with alkyl halides in the presence of KOH in absolute meth-

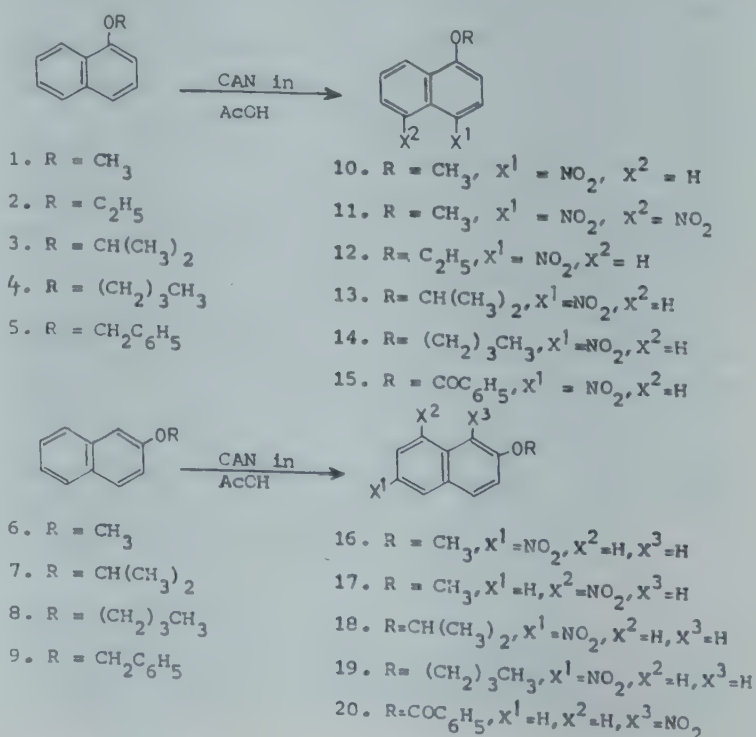


Table 1—Products of Reaction of Alkoxynaphthalene with Cerium(IV) Ammonium Nitrate

Starting Compound	Product, PMR(CDCl <sub>3</sub> ) <sup>a</sup> ; MS ( <i>m/z</i> , relative intensity %) <sup>b</sup>	Reaction time (h)	m.p. <sup>d</sup> (lit m.p. °C) <sup>e</sup>	Eluent	Yield <sup>c</sup> %
1	<b>10</b> ; δ 4.1 ( <i>s</i> , 3H), 7.8 ( <i>m</i> , 6H); 203 (100.0), 173 (38.9), 157 (30.2), 142 (27.1), 114 (84.8)	1	79(80)	Pet. ether	99.0
2	<b>11</b> ; δ 4.35 ( <i>s</i> , 3H), 7.6 ( <i>m</i> , 5H) <b>12</b> ; δ 1.4 ( <i>t</i> , 3H), 4.2 ( <i>q</i> , 2H), 7.7 ( <i>m</i> , 6H); 217 (100.0), 189 (36.0), 159 (43.3), 131 (30.4), 115 (69.6)	1	213(216) 115(116)	Pet. ether-benzene (9:1) Pet. ether	60.0
3	<b>13</b> <sup>c</sup> ; δ 1.6 ( <i>d</i> , 6H), 4.8 ( <i>m</i> , 1H), 6.85 ( <i>d</i> , 1H), ( <i>d</i> , 1H), 7.65 ( <i>m</i> , 2H), 8.4 ( <i>d</i> , 2H) 8.9 ( <i>d</i> , 1H); 231 (22.5), 190 (92.5), 143 (17.5), 131 (75), 115 (22.5)	2	Liquid	Pet. ether	88.8
4	<b>14</b> <sup>c</sup> ; δ 1.01 ( <i>t</i> , 3H), 1.75 ( <i>m</i> , 4H), 4.2 ( <i>t</i> , 2H), 5.75 ( <i>d</i> , 1H) 7.5 ( <i>m</i> , 2H), 8.24 ( <i>d</i> , 2H), 8.5 ( <i>d</i> , 1H); 245 (37.5), 189 (100.0), 159 (12.5), 115 (20.0)	2	-do-	Pet. ether	90.7
5	<b>15</b> ; δ 7.7 ( <i>m</i> , 11H); 293 (90.0), 248 (65.8), 247 (24.6), 106 (100.0)	1.5	170(172)	Pet. ether-benzene (8:2)	94.0
6	<b>16</b> ; δ 3.9 ( <i>s</i> , 3H), 7.7 ( <i>m</i> , 6H); 203 (6.1), 173 (1.5), 157 (2.0), 142 (12.8) <b>17</b> ; δ 4.0 ( <i>s</i> , 3H), 7.7 ( <i>m</i> , 6H)	1.5	134(136)	Pet. ether-benzene (8:2)	68.2
7	<b>18</b> <sup>c</sup> ; δ 1.45 ( <i>d</i> , 6H), 4.8 ( <i>m</i> , 1H), 7.2-8.1 ( <i>m</i> , 6H); 231 (93.5) 189 (98.9), 172 (21.2), 132 (81.7), 115 (100.0)	2	62-69(69) 58	Pet. ether-benzene (9:1) Pet. ether	75.0
8	<b>19</b> <sup>c</sup> ; δ 1.0 ( <i>t</i> , 3H), 1.75 ( <i>m</i> , 4H), 4.2 ( <i>t</i> , 2H), 7.2-8.0 ( <i>m</i> , 6H); 245 (100.0), 189 (87.5), 172 (22.5), 159 (35.0), 143 (87.5), 115 (99.0)	2.5	Liquid	Pet. ether	98.1
9	<b>20</b> ; δ 7.8 ( <i>m</i> , 11H); 293 (35.5), 247 (21.7), 130 (6.9), 106 (78.1)	1.5	140(141)	Pet. ether-benzene (8:2)	97.0

a, PMR were recorded on FT NMR, Jeol [JNM-FX 100] spectrometer; b, mass spectra were recorded on Jeol spectrometer at 70 eV; c, yields are unoptimised and refer to isolated yields; d, melting points are uncorrected; e, new compounds are **13**, **14**, **18**, **19**.

anol<sup>7</sup>. The following alkoxynaphthalenes were prepared: 1-methoxynaphthalene (**1**), 1-ethoxynaphthalene (**2**), 1-isopropoxynaphthalene (**3**), 1-butoxynaphthalene (**4**), 1-benzyloxynaphthalene (**5**), 2-methoxynaphthalene (**6**), 2-isopropoxynaphthalene (**7**), 2-butoxynaphthalene (**8**) and 2-benzyloxynaphthalene (**9**).

#### Functionalization of alkyl aryl ethers

The following general procedure as applied for derivatisation of **7** was used in all the cases.

To a solution of **7** (4g, 0.01 mol) in gl. acetic acid (10 ml) was added a saturated solution of cerium(IV) ammonium in gl. acetic acid (10 ml) dropwise during 1 hr. After keeping the reaction-mixture at room temperature for sometime it was heated on a water-bath at 60-80°C for 1 hr more. The progress of the reaction was monitored by TLC (silica gel, pet. ether-benzene, 7:3) and when the reaction was complete it was poured onto crushed ice and extracted with pet. ether (60-80°). The pet. ether extract was concentrated under reduced pressure and subjected to column chromatography (silica gel, 80 g) using pet. ether as an eluent. Removal of solvent gave yellow coloured

prisms of **18**, m.p. 58°; IR(KBr) cm<sup>-1</sup>: 1640, 1520, 1350; PMR(CDCl<sub>3</sub>): δ 1.45 (*d*, 6H), 4.8 (*m*, 1H), 7.25-8.1 (*m*, 6H); MS (*m/z* relative intensity; %): 231 (83.5), 190 (46.2) 189 (98.9), 172 (21.2), 159 (23.5), 143 (46.2), 115 (100.0). The compound was identified as 2-isopropoxy-6-nitronaphthalene.

The other nitro derivatives obtained from the alkoxynaphthalene (**1-6**, **8** and **9**) are listed in Table 1.

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## A Simple & Expedient Synthesis of Bis(pyrido[1,2-*a*]azepines)<sup>†</sup>

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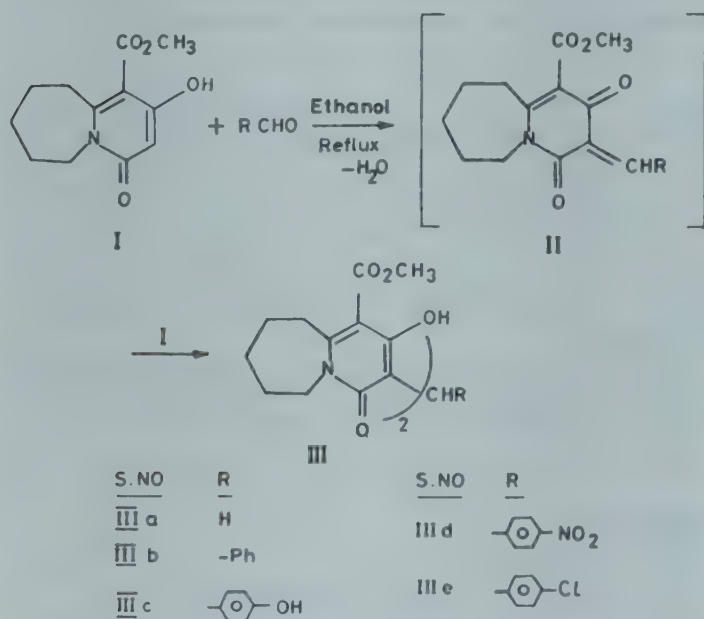
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Pyridoazepines (I) react with various aldehydes in refluxing ethanol to yield bis(pyrido[1,2-*a*]azepines) in low to moderate yields.

One of us earlier reported a novel synthesis of pyridoazepines and some of their reactions<sup>1</sup>. In this note we describe a facile reaction of these pyridoazepines with various aldehydes (carbonyl electrophiles) leading to the formation of apparently unknown 1,1-bis(4,6,7,8,9,10-hexahydro-1-methoxycarbonyl-2-hydroxy-4-oxo-pyrido[1,2-*a*]azepin-3-yl)methane (IIIa) and analogues (IIIb-e).

Thus pyridoazepine (I) reacted with various aldehydes in refluxing ethanol to yield bis(pyridoazepines) (III) in low to moderate yields (Scheme 1). Attempts to improve the yield through the use of acidic or basic catalysts were fruitless. The structures of the



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Table 1—Characterization Data of Various Bis(pyridoazepines) (III)<sup>a</sup>

Compd	Mol. formula	Found (calc.), %	m.p. (°C)	Yield (%)
IIIa	C <sub>25</sub> H <sub>30</sub> N <sub>2</sub> O <sub>8</sub>	C, 62.05 (61.71) H, 62.4 (6.22) N, 6.08 (5.76)	280	47
IIIb	C <sub>31</sub> H <sub>34</sub> N <sub>2</sub> O <sub>8</sub>	C, 65.91 (66.18) H, 5.74 (6.09) N, 5.36 (4.98)	320-22	39
IIIc	C <sub>31</sub> H <sub>34</sub> N <sub>2</sub> O <sub>9</sub>	C, 64.60 (64.35) H, 6.23 (5.92) N, 5.09 (4.84)	310-12	21
IIId	C <sub>31</sub> H <sub>33</sub> N <sub>3</sub> O <sub>10</sub>	C, 61.37 (61.28) H, 5.82 (5.47) N, 6.54 (6.92)	275-77	18
IIIe	C <sub>31</sub> H <sub>33</sub> ClN <sub>2</sub> O <sub>8</sub>	C, 62.58 (62.36) H, 5.78 (5.57) N, 4.70 (4.69)	293-95	20

<sup>a</sup>Very similar PMR spectra were obtained. PMR data ( $\delta$ -values) of representative IIIa: 1.75 (12H, bs), 2.75 (4H, bs), 3.65 (2H, s), 3.9 (6H, s), 4.35 (4H, s), and 12.27 (2H, bs); and for IIIb, 1.70 (12H, bs), 2.80 (4H, bs), 3.85 (6H, s), 4.35 (4H, s), 6.1 (1H, s), 7.15 (5H) and 11.93 (2H, bs).

product, IIIa-f, were proved by elemental analyses and spectral data (Table 1). In rationalising the formation of III, we believe that the intermediate II, formed from I and RCHO, undergoes rapid Michael addition with I to yield III (see Scheme 1).

Attempted reactions of I with other carbonyl electrophiles such as dimethyl acetylenedicarboxylate or arylisocyanates were unsuccessful.

Melting points reported are uncorrected.

### Bis(pyridoazepines) (III)

Pyridoazepine (I) and the aldehyde were mixed in molar proportions in ethanol and the mixture refluxed overnight. On cooling, the product bis(pyridoazepine) precipitated; this was filtered and recrystallized. If the product did not precipitate, the solvent was removed at the rotary evaporator and the residue recrystallized from benzene to yield analytically pure product.

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# Benzoxadiazines: Part IV—Syntheses of Oxadiazino[5,6-*b*]phenazines & Pyrazolo[4,5-*a*]phenazines

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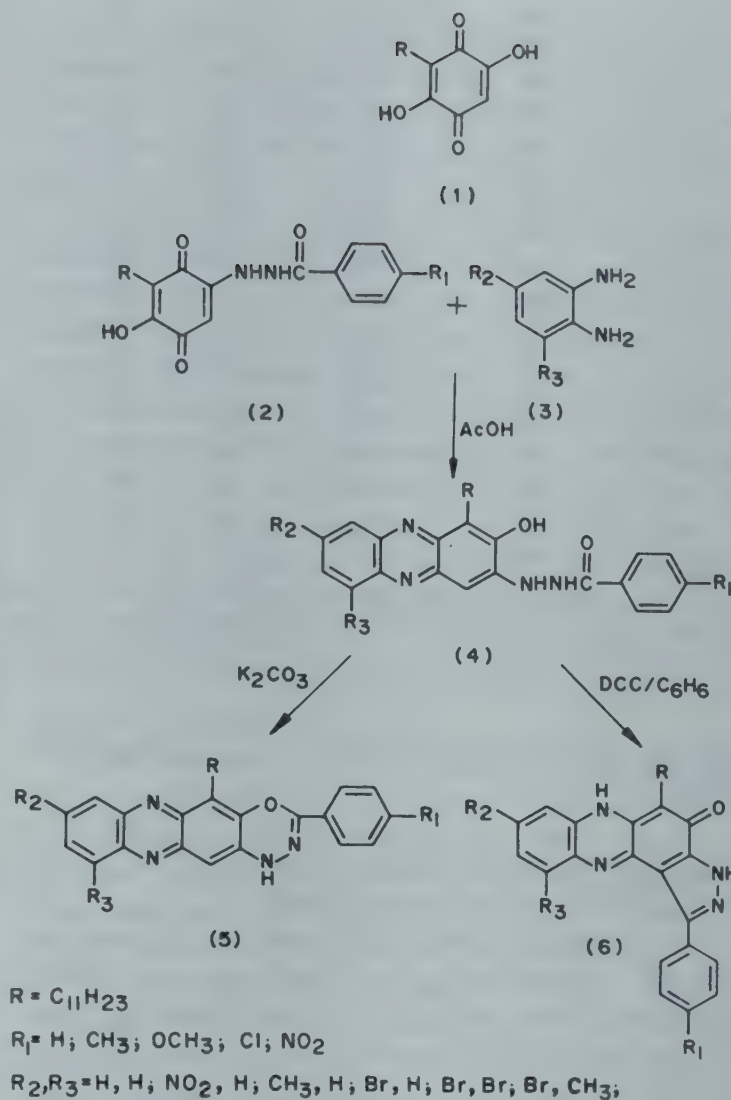
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N'-(5-Hydroxy-6-undecyl-*p*-benzoquinon-2-yl)arylhydrazide (2) has been condensed with various substituted *o*-phenylenediamines (3) to get 2-(3-hydroxy-4-undecyl-2-phenazinyl)arylhydrazides (4). Compound 4 on treatment with anhydrous potassium carbonate in acetone affords oxadiazino[5,6-*b*]phenazines (5), whereas with dicyclohexylcarbodiimide in dry benzene yields pyrazolo[4,5-*a*]phenazines (6).

Condensation reactions of 2,5-dihydroxy-6-undecyl-1,4-benzoquinone (1), commonly known as embelin; with *o*-aminophenol<sup>1</sup>, *o*-phenylenediamines<sup>2</sup> and aromatic acid hydrazides<sup>3</sup> were reported by the authors earlier. The reaction of 1 with aromatic acidhydrazides was shown to yield N'-(5-hydroxy-6-undecyl-*p*-benzoquinon-2-yl)arylhydrazide (2) as one of the products. Since 2 has a reactive *o*-hydroxy carbonyl function, we were prompted to investigate its cyclisation reactions.

Compound 2 on treatment with *o*-phenylenediamines (3) afforded 2-(3-hydroxy-4-undecyl-2-phenazinyl)benzohydrazides (4) (Scheme 1). With a view to developing 1,3,4-oxadiazine ring system, an attempt was made to subject 4a-j to cyclodehydration using such reagents as (a) alcohol-sulphuric acid, (b) acetic acid-sulphuric acid, (c) polyphosphoric acid, (d) anhydrous potassium carbonate and (e) dicyclohexylcarbodiimide. With reagents a-c no products could be isolated. However, the reaction of 4e-j with anhydrous potassium carbonate in dry acetone resulted in a dark brown product, which crystallised from benzene to give 1*H*-3-aryl-5-undecyl[1,3,4]oxadiazino[5,6-*b*]phenazines (5e-j) (Table 1). Compound 4a and 4b when refluxed with DCC in dry benzene yielded greenish yellow crystals characterised as 1*H*,9*H*-3-aryl-10-undecylpyrazolo[4,5-*a*]phenazine-11-ones (6a,b). The formation of 5 can be attributed due to the possible oxyanion generation and further cyclisation in basic medium. In neutral medium the tautomeric quinonoid structure provides elements of water which are lost forming 6.



SCHEME 1

Structures of compounds 4-6 were established by elemental analysis and spectral data. Structures of 4a-j have also been confirmed by the preparation of their acetyl derivatives. Compounds 5 and 6 gave negative ferric reaction.

Melting points were determined in open capillaries and are uncorrected. The homogeneity of the compounds is checked by TLC on silica gel.

## General procedure for 1*H*-3-aryl-5-undecyl[1,3,4]-2-phenazinyl)arylhydrazides (4a-j)

To a soluble of 2 (0.01 mol) in warm gl. acetic acid (20 ml) was added a solution of *o*-phenylenediamine (0.01 mol) in acetic acid (15 ml) and refluxed with stirring for 3 hr. The reaction mixture was cooled, poured onto crushed ice, the separated red coloured solid filtered, dried and crystallised from suitable solvent (Table 1). Characteristic spectral data of the compound 4a: IR(Nujol): 3320 (NH), 3200 (OH) and 1640 cm<sup>-1</sup> (NHCO);

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Table 1—Physical & Analytical Data of the Compounds **4a** to **6b**

Compd**	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Mol formula	Yield (%)	M.P. (°C)
<b>4a</b>	H	H	H	C <sub>30</sub> H <sub>36</sub> N <sub>4</sub> O <sub>2</sub>	60	135
<b>4b</b>	CH <sub>3</sub>	H	H	C <sub>31</sub> H <sub>38</sub> N <sub>4</sub> O <sub>2</sub>	60	160
<b>4c</b>	OCH <sub>3</sub>	H	H	C <sub>31</sub> H <sub>38</sub> N <sub>4</sub> O <sub>3</sub>	62	150
<b>4d</b>	Cl	H	H	C <sub>30</sub> H <sub>35</sub> N <sub>4</sub> O <sub>2</sub> Cl	65	154
<b>4e</b>	NO <sub>2</sub>	H	H	C <sub>30</sub> H <sub>35</sub> N <sub>5</sub> O <sub>4</sub>	55	148
<b>4f</b>	NO <sub>2</sub>	NO <sub>2</sub>	H	C <sub>30</sub> H <sub>34</sub> N <sub>6</sub> O <sub>6</sub>	55	165
<b>4g</b>	NO <sub>2</sub>	CH <sub>3</sub>	H	C <sub>31</sub> H <sub>37</sub> N <sub>5</sub> O <sub>4</sub>	58	150
<b>4h</b>	NO <sub>2</sub>	Br	H	C <sub>30</sub> H <sub>34</sub> N <sub>5</sub> O <sub>4</sub> Br	58	148
<b>4i</b>	NO <sub>2</sub>	Br	Br	C <sub>30</sub> H <sub>33</sub> N <sub>5</sub> O <sub>4</sub> Br <sub>2</sub>	57	139
<b>4j</b>	NO <sub>2</sub>	CH <sub>3</sub>	Br	C <sub>31</sub> H <sub>36</sub> N <sub>5</sub> O <sub>4</sub> Br	60	161
<b>5e</b>	NO <sub>2</sub>	H	H	C <sub>30</sub> H <sub>33</sub> N <sub>5</sub> O <sub>3</sub>	60	150
<b>5f</b>	NO <sub>2</sub>	NO <sub>2</sub>	H	C <sub>30</sub> H <sub>32</sub> N <sub>6</sub> O <sub>5</sub>	55	145
<b>5g</b>	NO <sub>2</sub>	CH <sub>3</sub>	H	C <sub>31</sub> H <sub>35</sub> N <sub>5</sub> O <sub>3</sub>	50	140
<b>5h</b>	NO <sub>2</sub>	Br	H	C <sub>30</sub> H <sub>32</sub> N <sub>5</sub> O <sub>3</sub> Br	52	142
<b>5i</b>	NO <sub>2</sub>	Br	Br	C <sub>30</sub> H <sub>31</sub> N <sub>5</sub> O <sub>3</sub> Br <sub>2</sub>	50	144
<b>5j</b>	NO <sub>2</sub>	CH <sub>3</sub>	Br	C <sub>31</sub> H <sub>34</sub> N <sub>5</sub> O <sub>3</sub> Br	48	140
<b>6a</b>	H	H	H	C <sub>30</sub> H <sub>34</sub> N <sub>4</sub> O	50	142
<b>6b</b>	CH <sub>3</sub>	H	H	C <sub>31</sub> H <sub>36</sub> N <sub>4</sub> O	45	138

\*\*All the compounds synthesised gave satisfactory elemental analyses. Compounds **4a**, **4b**, **4d** to **4j** were recrystallised from ethanol; **4c** from acetic acid; and **5e** to **5j** and **6a**, **6b** from benzene.

MS:  $m/z$ : 484, 365, 350, 225, 132, 120 and 105 (100).

*General procedure for 1H-3-aryl-5-undecyl[1,3,4]-oxadiazino[5,6-b]phenazines (5e-j)*

To a solution of **4e-j** (0.01 mol) in dry acetone (50 ml), anhydrous potassium carbonate (0.02 mol) was added and refluxed for 38-46 hr. The hot reaction mixture was filtered, solvent distilled off and residue treated with ice and dil HCl. The solid separated was filtered and washed with excess water. The dry compound was crystallised from appropriate solvent (Table 1). Characteristic spectral data of compound **5e**: IR(Nujol): 3310 (NH) and 1210  $\text{cm}^{-1}$  (C-O-C); PMR(DMSO- $d_6$ ):  $\delta$  0.9 (*t*, 3H, CH<sub>3</sub>), 1.25 (*m*, 18H, alkyl side chain), 2.5 (*t*, 2H, allylic), 4.5 (*s*, 1H, NH) and 7.5 to 8.2 (*m*, 9H, aromatic).

*General procedure for 1H,9H-3-aryl-10-undecyl-pyrazolo[4,5-a]phenazin-11-ones (6a,b)*

Compounds **4a,b** (0.01 mol) were taken separ-

ately in dry benzene (50 ml) and to the solution was added DCC (0.01 mol) and the mixtures refluxed for 4 hr. After removing the solvent, the residue was triturated with ether followed by ethanol to get greenish yellow crystals. It was filtered off, dried and recrystallised from respective solvents (Table 1). Characteristic spectral data of compound **6a**: IR(nujol): 3220 (NH) and 1680  $\text{cm}^{-1}$  (CO); PMR(CDCl<sub>3</sub>):  $\delta$  0.9 (*t*, 3H, CH<sub>3</sub>), 1.25 (*m*, 18H, alkyl side chain), 3.0 (*t*, 2H, allylic), 3.5 (*b*, 1H, NH), 7.0-7.7 (*m*, 9H, aromatic) and 12.4 (*b*, 1H, pyrazolyl NH).

The authors wish to thank the CSIR, New Delhi for financial help.

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## Reaction of Thiobarbituric Acid & Hydrazine: Formation of a Secondary Amine

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Reaction of 2-methylmercaptobarbituric acid (**2**) with hydrazine leads to a secondary amine, 2,2-bis(3,4,5,6-tetrahydropyrimidinyl)amine (**4**) instead of *s*-trihydrazinopyrimidine. A plausible mechanism is proposed for the formation of **4**.

Thiobarbituric acid (**1**, TBA) has been used as a synthon component for obtaining a series of pharmacologically important compounds. While attempting the synthesis of a trihydrazinopyrimidine by the reaction of *S*-methylmercaptobarbituric acid (**2**), derivable from **1**, and hydrazine hydrate we isolated a secondary amine. In this note we report its characterisation and also a plausible mechanism of its formation.

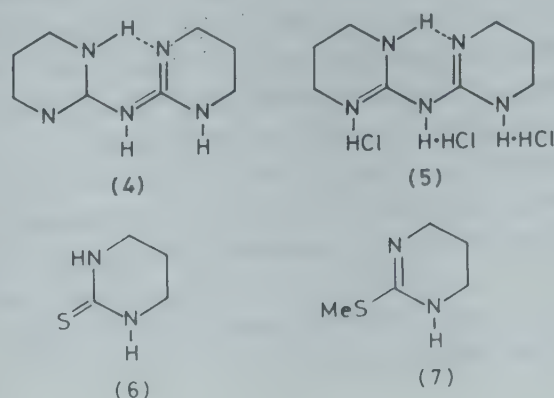
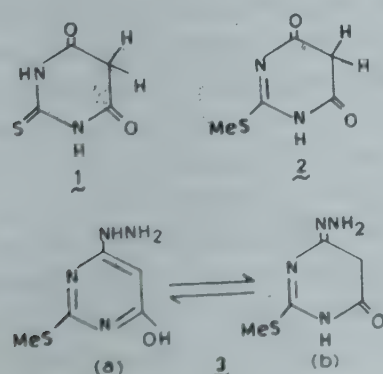
Thiobarbituric acid was *S*-methylated with methyl iodide in acetone to give the 2-methylmercaptobarbituric acid (**2**). Treatment of **2** (0.316 g, 0.002 mol) with 60% hydrazine hydrate (0.058 g) in methanol (10 ml) at room temperature for 30 min led to a white compound which recrystallised from hot water; m.p. > 260°; yield 92%. It was characterised as the monohydrazone (**3**) on the basis of its spectral and analytical data (Found: C, 34.3; H, 4.5; N, 32.0; S, 18.3.  $C_5H_8N_4OS$  requires C, 34.8; H, 4.7; N, 32.6; S, 18.6%); IR(KBr): 1610 (C=N), 2880 (aliphatic CH), 3020 (Ar-CH), 3080 (NH), 3280 (NH<sub>2</sub>), 3440 cm<sup>-1</sup> (enolic OH)<sup>1,2</sup>; PMR (DMSO-*d*<sub>6</sub>): δ 2.47 (s, 3H, SMe), 4.47 (s, 2H, CH<sub>2</sub>), 8.1 (b, 3H, NHNH<sub>2</sub>, exchangeable with D<sub>2</sub>O). The signals in the range δ 7.0-10.0 were totally exchangeable with D<sub>2</sub>O, indicat-

ing the absence of aromatic proton. The mass fragmentation pattern also lent support to structure (**3**). This difference in behaviour in IR and PMR may be due to the existence of the monohydrazone (**3**) in its tautomeric forms **3a** and **3b**.

Compound **3** (0.86 g, 0.005 mol) was further refluxed with 60% hydrazine hydrate (4 ml) in ethanol (20 ml) till methylmercaptan ceased to evolve (60-70 hr). Upon removal of the solvent an oil was obtained, which could be converted into its hydrochloride by treatment with conc hydrochloric acid. It was recrystallised from ethanol; m.p. 92°, yield 70% (Found: C, 17.4; H, 4.1; N, 24.2.  $C_8H_{18}N_5Cl_3$  requires C, 17.1; H, 3.6; N, 24.1%); IR (KBr): 1630 (C=N), 2880 (aliphatic CH), 3140 (NH, H-bonded), 3240 cm<sup>-1</sup> (free NH<sub>2</sub>); MS: *m/z* 181 ( $C_8H_{15}N_5$ )<sup>+</sup> (*M*<sup>+</sup> - 3HCl), 105 ( $C_2H_{11}N_5$ )<sup>+</sup>, 71 ( $C_2H_5N_3$ )<sup>+</sup>, 69 ( $C_2H_3N_3$ )<sup>+</sup>, 44 ( $CH_4N_2$ , base peak)<sup>+</sup>.

However, the oil also solidified after keeping the same in cold (4°C) for about a week. The solid obtained was recrystallised from ethanol to give the free base, m.p. 150°, yield 77%. The free base analysed for  $C_8H_{15}N_5$  (Found: C, 54.0; H, 9.0; N, 38.8. Req'd: C, 53.0; H, 8.2; N, 38.7%).

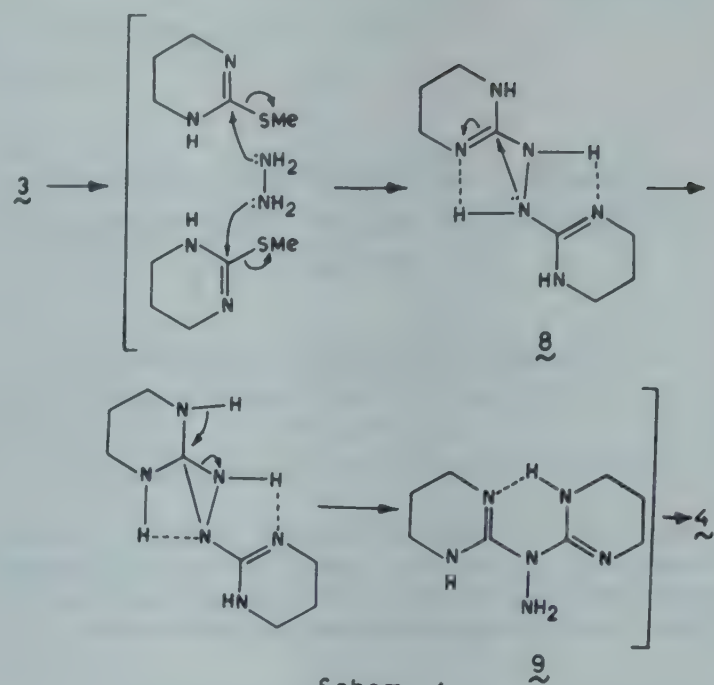
The IR spectrum of the free base showed H-bonded NH peak in the region 3120-3160 and free NH at 3220 cm<sup>-1</sup>. The elemental analyses and IR data were in favour of structure (**4**) for the base and (**5**) for the hydrochloride. Estimation of chloride also indicated the presence of three chloride ions in the molecule. The mass spectral data of the hydrochloride was also clearly in favour of the structure (**5**). Further the free base (**4**) could also be obtained in 60% on refluxing 2-methylmercapto-3,4,5,6-tetrahydropyrimidine (**7**, 0.52 g, 0.004 mol) with 60% hydrazine hydrate (3 ml) in ethanol till evolution of methylmercaptan ceased (60-70 hr). Removal of ethanol left a pale yellow liquid which on standing for a week in the cold



7<sup>10</sup> afforded **4**, m.p. 145-50°. The tetrahydropyrimidine (**7**) was obtained by methylation of 2-thio-3,4,5,6-tetrahydropyrimidine (**6**)<sup>3</sup> with methyl iodide.

The mechanism of formation of **4** can be explained as follows: Hydrazine behaves as a good reducing agent (Wolff-Kischner reduction) for the reduction of  $>C=O$  to  $>CH_2$ . Hence it reduced **3** forming 2-methylmercapto-3,4,5,6-tetrahydropyrimidine (**7**) as an intermediate. Two mol of **7** reacted with one mol of hydrazine to form the hydrazino derivative (**8**) which is stabilised due to H-bonds. Compound (**8**) underwent rearrangement to form a disubstituted (unsymmetrical) hydrazine (**9**) involving a diaziridine intermediate; **9** underwent further reduction to form the base (**4**) (Scheme 1). This mechanism is also supported by a synthesis of **7** from 1,3-diaminopropane and  $CS_2$  and its subsequent reaction with hydrazine to give **4** and **5**.

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## Synthesis of Some 6-Substituted Aminopyridin-2(*H*)-ones & Their Derivatives

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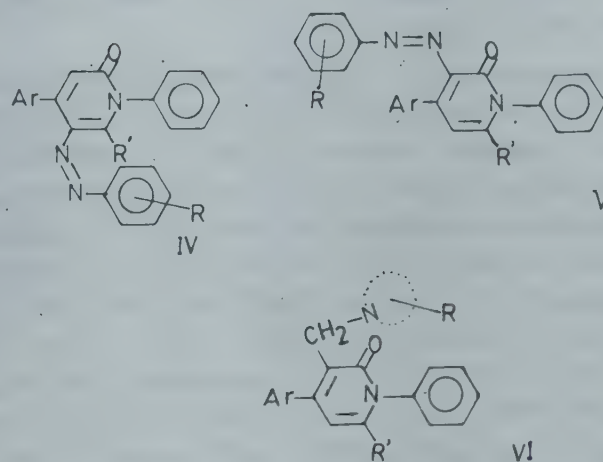
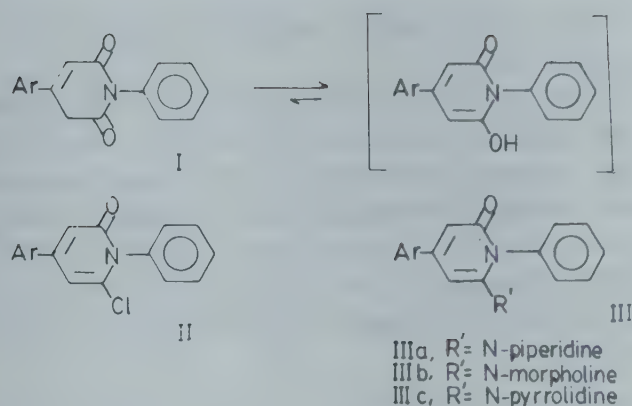
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6-Substitutedamino-4-(4-methoxyphenyl)-1-phenyl-2(*H*)-pyridinones (III a-c) have been obtained from 6-chloro-4-(4-methoxyphenyl)-1-phenyl-2(*H*)-pyridinone (II) which in turn is prepared from 4-(4-methoxyphenyl)-1-phenyl-5(*H*)-pyridin-2,6-dione (I). The aminopyridinones (III a-c) give 6-substitutedamino-4-(4-methoxyphenyl)-1-phenyl-5-(aryldiazo)-2(*H*)-pyridinones (IV) and 6-substitutedamino-4-(4-methoxyphenyl)-1-phenyl-3-(aryldiazo)-2(*H*)-pyridinones (V) on azo coupling reaction with aryldiazonium chlorides. However, the Mannich reaction on III gives only single product identified as 6-substitutedamino-4-(4-methoxyphenyl)-1-phenyl-3-(substituted aminomethyl)-2(*H*)-pyridinones (VI). All the compounds have been characterised by elemental analyses and IR, PMR and mass data.

Some 6-aminopyridin-2(*H*)-ones are reported to have antiinflammatory activity<sup>1-3</sup>. These compounds have also two nucleophilic centres<sup>4,5</sup>, viz. positions 3 and 5 and hence can act as good synthons. In spite of the importance of this class of compounds not many reports have appeared on their synthesis. Our interest in the biological activity associated with six-membered heterocycles in general and the title compounds in particular led us to devise a synthetic approach towards some 6-substituted-amino-4-(4-methoxyphenyl)-1-phenyl-2(*H*)-pyridinones (IIIa-c) and to study their reactions.

We have earlier synthesised 4-(4-methoxyphenyl)-1-aryl-5(*H*)-pyridine-2,6-diones (I) by the fusion of  $\beta$ -arylglutaconic acid with arylamines. The pyridindiones (I) exist in enol form so as to qualify themselves as the natural precursors for IIIa-c. When I (aryl = phenyl) was treated with phosphorus oxychloride it gave 6-chloro-4-(4-methoxyphenyl)-1-phenyl-2(*H*)-pyridinone (II). The chlorine atom in 6-position was then replaced by various cyclic secondary amines to get the title compounds (IIIa-c).

Compounds (IIIa-c) were subjected to azo-coupling reaction when two azo-coupled products were obtained, which were separated by column chroma-



Ar = *p*-methoxyphenyl ;

R' = N-piperidino for IVa-e; Va-e; VIa-c ;

R' = N-morpholino for IVf-j; Vf-j ; VI d-f.

tography over activated silica gel. The two compounds were characterised as 6-amino-4-(4-methoxyphenyl)-1-phenyl-5-(aryldiazo)-2(*H*)-pyridinone (IV) and its 3-aryldiazo isomer (V), on the basis of spectral data. In no case bis-coupled product was obtained. This may be due to the fact that once the azo group enters either of the position in III, the nucleophilicity of the other position is weakened.

Like in the azo coupling reaction, we envisaged that III on Mannich reaction may give two isomeric Mannich bases. However, the reaction resulted in the formation of only one product in which the aminomethyl group was introduced in 3-position. Thus using various secondary amines like piperidine, morpholine, pyrrolidine, the Mannich reaction with III gave 6-substitutedamino-4-(4-methoxyphenyl)-1-phenyl-3-(aminomethyl)-2(*H*)-pyridinones (VI) as the only products. It appears that the nucleophilicities of the two sites in III are not comparable in all reactions and position-3 is more nucleophilic<sup>6</sup> than position-5.

Melting points reported are uncorrected. IR spectra (KBr) were recorded on a Beckmann Accu

Lab-10 spectrophotometer ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ), PMR spectra on a Varian T 60 spectrometer using TMS as an internal standard (chemical shifts in  $\delta$ , ppm).

*6-Chloro-4-(4-methoxyphenyl)-1-phenyl-2(H)-pyridinone (II)*

A mixture of I (2.93 g, 0.01 mol) and phosphorous oxychloride (9 ml) was refluxed for 1 hr and poured onto crushed ice, when II was obtained as a solid. It was washed thoroughly with water and crystallized from ethanol or water, m.p. 185-86°, yield 2.5 g (80%) (Found: C, 69.1; H, 4.4; N, 4.5; Cl, 11.5%.  $\text{C}_{18}\text{H}_{14}\text{NO}_2\text{Cl}$  requires C, 69.2; H, 4.5; N, 4.5; Cl, 11.5%).

*4-(4-Methoxyphenyl)-1-phenyl-6-piperidino-2(H)-pyridinone (IIIa)*

A mixture of II (3.12 g, 0.01 mol) and piperidine (6 ml) was refluxed for 9 hr and thereafter steam distilled to remove excess of amine. The resultant solid was filtered, washed with water and crystallized from acetone to obtain IIIa, m.p. 175-76°, yield 2.6 g (72%) (Found: C, 76.6; H, 6.7; N, 7.8%.  $\text{C}_{23}\text{H}_{24}\text{O}_2\text{N}$  requires C, 76.7; H, 6.7; N, 7.8%); IR (KBr): 1675 ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ): 1.20 (bs, 6H,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$  of piperidine), 2.80 (m, 4H,  $-\text{CH}_2-\text{N}-\text{CH}_2$ ), 3.80 (s, 3H,  $-\text{OCH}_3$ ), 5.90 (s, 1H,  $\text{C}_5-\text{H}$ ), 6.50 (s, 1H,  $\text{C}_3-\text{H}$ ), 6.81-7.55 (m, 9H, Ar-H).

Compounds IIIb and IIIc were prepared in the same way.

IIIb: m.p. 200°, yield 2.8 g (77%) (Found: C, 72.8; H, 6.1; N, 7.7%.  $\text{C}_{22}\text{H}_{22}\text{O}_3\text{N}_2$  requires C, 72.9; H, 6.1; N, 7.7%); IR (KBr): 1640 ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ): 2.1-2.55 (m, 8H, morpholine-H), 3.8 (s, 3H,  $-\text{OCH}_3$ ), 5.0 (s, 1H,  $\text{C}_5-\text{H}$ ), 6.18 (s, 1H,  $\text{C}_3-\text{H}$ ), 6.9-7.6 (m, 9H, Ar-H).

IIIc: m.p. 156°, yield 2.49 g (69%) (Found: C, 76.2; H, 6.4; N, 8.1%.  $\text{C}_{22}\text{H}_{22}\text{O}_2\text{N}_2$  requires C, 76.3; H, 6.4; N, 8.1%); IR (KBr): 1655 ( $\text{C}=\text{O}$ ).

*4-(4-Methoxyphenyl)-1-phenyl-5-(phenylazo)-6-piperidino-2(H)-pyridinone (IVa) and 4-(4-methoxyphenyl)-1-phenyl-3-(phenylazo)-6-piperidino-2(H)-pyridinone (Va)*

To a precooled (0-5°) solution of IIIa (3.60g, 0.01 mol) in acetone (50 ml) was added a precooled (0-5°) solution of benzenediazonium chloride [prepared by diazotizing aniline (0.93g, 0.01 mol) in 6 ml of 1:1 HCl with  $\text{NaNO}_2$  (0.69g, 0.01 mol) in 10 ml water]. The reaction mixture was poured into water (200 ml) and basified with NaOH. The coloured product was filtered, washed with water and dried.

The above mixture was chromatographed over a column of activated silica gel (60-120 mesh). Elution

with  $\text{CHCl}_3$  gave IVa as a red compound. Subsequent elution with ethyl acetate gave Va as a red solid.

Compounds IVb-e and Vb-e were obtained by similar coupling with other aryldiazonium salts on II-1a. Azocoupling reaction of IIIb with aryldiazonium chlorides gave compounds IVf-j and Vf-j. These compounds are listed in Table 1. PMR and physical data of representative compounds IVa and Va are as follows.

IVa: m.p. 156°, yield 1.4g (30%) (Found: C, 74.9; H, 6.0; N, 12.2%.  $\text{C}_{29}\text{H}_{28}\text{O}_2\text{N}_4$  requires C, 75.0; H, 6.0; N, 12.1%); IR (KBr): 1650 ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ): 1.0 (m, 6H,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$  of piperidine), 2.9 (m, 4H,  $-\text{CH}_2-\text{N}-\text{CH}_2$  of piperidine), 3.8 (s, 3H,  $-\text{OCH}_3$ ), 6.3 (s, 1H,  $\text{C}_3-\text{H}$ ), 6.5-7.35 (m, 14H, Ar-H).

Va: m.p. 196-97°, yield 2g (43%) (Found: C, 74.9; H, 6.0; N, 12.2%.  $\text{C}_{29}\text{H}_{28}\text{O}_2\text{N}_4$  requires C, 75.0; H, 6.0; N, 12.1%); PMR ( $\text{CDCl}_3$ ): 1.3 (m, 6H,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$  of piperidine), 2.9 (m, 4H,  $-\text{CH}_2-\text{N}-\text{CH}_2$ ), 3.8 (s, 3H,  $-\text{OCH}_3$ ), 5.85 (s, 1H,  $\text{C}_5-\text{H}$ ), 6.5-7.8 (m, 14H, Ar-H).

*4-(4-Methoxyphenyl)-1-phenyl-6-piperidino-3-(1-piperidinylmethyl)-2(H)-pyridinone (VIa)*

A mixture of paraformaldehyde (0.3g, 0.01 mol) and piperidine (0.85 ml, 0.01 mol) was refluxed for 45 min in chlorobenzene (50 ml). IIIa (3.60g, 0.01 mol) was then added to the reaction mixture, refluxed for 22 hr and steam distilled to remove chlorobenzene, when VIa separated out. It was filtered, washed with water and crystallized from acetone, m.p. 185-86°, yield 3.0 g (65%) (Found: C, 76.1; H, 7.6; N, 9.1%.  $\text{C}_{29}\text{H}_{35}\text{O}_2\text{N}_3$  requires C, 76.2; H, 7.7; N, 9.2%); IR (KBr): 1640 ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ): 1.33 (bs, 6H,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2$  of piperidine at 6-position), 1.45 (bs, 6H,  $-\text{CH}_2-\text{CH}_2-\text{CH}_2$  of piperidine at 3-position), 2.4 (m, 4H,  $-\text{CH}_2-\text{N}-\text{CH}_2$  of position 6-piperidine), 2.75 (m, 4H,  $-\text{CH}_2-\text{N}-\text{CH}_2$  of position 3-piperidine), 3.25 (s, 2H,  $-\text{CH}_2$ ), 3.9 (s, 3H,  $-\text{OCH}_3$ ), 5.75 (s, 1H,  $\text{C}_5-\text{H}$ ), 6.9-7.8 (m, 9H, Ar-H).

Similar reaction of IIIa with morpholine and pyrrolidine yielded VIb, c while those of IIIb with piperidine, morpholine, and pyrrolidine afforded VI d-f respectively. Physical and spectral data of VI b-f are as follows.

VIb: m.p. 185°, yield 3.2g (70%) (Found: C, 73.1; H, 7.2; N, 9.0%.  $\text{C}_{28}\text{H}_{33}\text{O}_3\text{N}_3$  requires C, 73.2; H, 7.2; N, 9.2%); IR (KBr): 1640 ( $\text{C}=\text{O}$ ).

VIc: m.p. 160°, yield 2.0g (45%) (Found: C, 75.8; H, 7.4; N, 9.4%.  $\text{C}_{28}\text{H}_{33}\text{O}_2\text{N}_3$  requires C, 75.9; H, 7.5; N, 9.5%); IR (KBr): 1640 ( $\text{C}=\text{O}$ ).

Table 1 — Characterization Data of 4-(4-Methoxyphenyl)-6-piperidino-1-phenyl-5-(arylozo)-2(*H*)-pyridinones (IVa-j) and 4-(4-methoxyphenyl)-6-piperidino-1-phenyl-3-(arylozo)-2(*H*)-pyridinones (Va-j)

Compd	R	m.p. (°C)	Yield* (%)	Mol formula	N (%)†	
					Found	Calc.
Compounds obtained by azo-coupling with IVa						
IVa	H	156	30	C <sub>29</sub> H <sub>28</sub> O <sub>2</sub> N <sub>4</sub>	12.2	12.1
IVb	<i>m</i> -Cl	170	36	C <sub>29</sub> H <sub>27</sub> O <sub>2</sub> N <sub>4</sub> Cl	11.1	11.2
IVc	<i>p</i> -Cl	190	37	C <sub>29</sub> H <sub>27</sub> O <sub>2</sub> N <sub>4</sub> Cl	11.1	11.2
IVd	<i>m</i> -NO <sub>2</sub>	170	33	C <sub>29</sub> H <sub>27</sub> O <sub>4</sub> N <sub>5</sub>	13.9	13.8
IVe	<i>p</i> -CH <sub>3</sub>	148	29	C <sub>30</sub> H <sub>30</sub> O <sub>2</sub> N <sub>4</sub>	11.7	11.7
Va	H	196	43	C <sub>29</sub> H <sub>28</sub> O <sub>2</sub> N <sub>4</sub>	12.2	12.1
Vb	<i>m</i> -Cl	202	38	C <sub>29</sub> H <sub>27</sub> O <sub>2</sub> N <sub>4</sub> Cl	11.1	11.2
Vc	<i>p</i> -Cl	200	40	C <sub>29</sub> H <sub>27</sub> O <sub>2</sub> N <sub>4</sub> Cl	11.1	11.2
Vd	<i>m</i> -NO <sub>2</sub>	210	29	C <sub>29</sub> H <sub>27</sub> O <sub>4</sub> N <sub>5</sub>	13.9	13.8
Ve	<i>p</i> -CH <sub>3</sub>	158	34	C <sub>30</sub> H <sub>30</sub> O <sub>2</sub> N <sub>4</sub>	11.7	11.7
Compounds obtained by azo-coupling with IIIb						
IVf	H	160	39	C <sub>28</sub> H <sub>26</sub> O <sub>3</sub> N <sub>4</sub>	12.0	12.0
IVg	<i>m</i> -Cl	175	36	C <sub>28</sub> H <sub>25</sub> O <sub>3</sub> N <sub>4</sub> Cl	11.1	11.2
IVh	<i>p</i> -Cl	176	36	C <sub>28</sub> H <sub>25</sub> O <sub>3</sub> N <sub>4</sub> Cl	11.1	11.2
IVi	<i>m</i> -NO <sub>2</sub>	174	33	C <sub>28</sub> H <sub>25</sub> O <sub>5</sub> N <sub>5</sub>	13.6	13.7
IVj	<i>p</i> -CH <sub>3</sub>	145	29	C <sub>29</sub> H <sub>28</sub> O <sub>3</sub> N <sub>4</sub>	11.6	11.7
Vf	H	182	43	C <sub>28</sub> H <sub>26</sub> O <sub>3</sub> N <sub>4</sub>	12.0	12.0
Vg	<i>m</i> -Cl	195	38	C <sub>28</sub> H <sub>25</sub> O <sub>3</sub> N <sub>4</sub> Cl	11.1	11.2
Vh	<i>p</i> -Cl	195	38	C <sub>28</sub> H <sub>25</sub> O <sub>3</sub> N <sub>4</sub> Cl	11.1	11.2
Vi	<i>m</i> -NO <sub>2</sub>	222	30	C <sub>28</sub> H <sub>25</sub> O <sub>5</sub> N <sub>5</sub>	13.7	13.7
Vj	<i>p</i> -CH <sub>3</sub>	162	36	C <sub>29</sub> H <sub>28</sub> O <sub>3</sub> N <sub>4</sub>	11.6	11.7

\*Yield is based on the weight of III

†Satisfactory C, H, analyses were obtained for all the compounds

IVd: m.p. 190°, yield 3.2g (70%) (Found: C, 73.1; H, 7.2; N, 9.1%. C<sub>28</sub>H<sub>33</sub>O<sub>3</sub>N<sub>3</sub> requires C, 73.2; H, 7.2; N, 9.2%); IR (KBr): 1640 (>C=O); PMR (CDCl<sub>3</sub>): 1.43 (*m*, 6H, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-of piperidine), 2.47 (*t*, 4H, -CH<sub>2</sub>-N-CH<sub>2</sub> of piperidine), 2.8 (*t*, 4H, CH<sub>2</sub>-N-CH<sub>2</sub> of morpholine), 3.25 (*m*, 6H, CH<sub>2</sub>-O-CH<sub>2</sub> and Ar-CH<sub>2</sub>-N), 3.85 (*s*, 3H, -OCH<sub>3</sub>), 5.72 (*s*, 1H, C<sub>5</sub>H), 6.85-7.75 (*m*, 9H, Ar-H).

IVe: m.p. 180°, yield 3.4g (73%) (Found: C, 70.2; H, 6.7; N, 9.1%. C<sub>27</sub>H<sub>31</sub>O<sub>4</sub>N<sub>3</sub> requires C, 70.3; H, 6.7; N, 9.1%); IR (KBr): 1640 (>C=O).

IVf: m.p. 192°, yield 2.4g (54%) (Found: C, 72.7; H, 7.0; N, 9.4%. C<sub>27</sub>H<sub>31</sub>O<sub>3</sub>N<sub>3</sub> requires C, 72.8; H, 7.0; N, 9.4%); IR (KBr): 1640 (>C=O).

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## A Novel Synthesis of N-Substituted 3-Acylamino-2-oxo-1,2-dihydroquinoline-4-carboxamides

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Isothiocyanate-mediated condensation of N-acylglycines (**1**) with isatins (**2**) affords N-substituted 3-acylamino-2-oxo-1,2-dihydroquinoline-4-carboxamides (**4**) which are also obtained by the reaction of 2-aryl-2-oxazolin-5-ones (**6**) with isatinimines (**5**).

In an earlier work from this laboratory, a one-pot synthesis of disubstituted 4-arylmethylene-2-imidazolin-5-ones involving isothiocyanate-mediated condensation of N-acyl- $\alpha$ -amino acids with aromatic aldehydes was reported<sup>1</sup>. Presently we have observed that a similar condensation of N-acyl- $\alpha$ -amino acids (**1**) with isatins (**2**), using pyridines as a catalyst, leads to N-substituted 3-acylamino-2-oxo-1,2-dihydroquinoline-4-carboxamides (**4**) together with isatinimines (**5**).

In order to probe the reaction mechanism, the hitherto unknown azlactone (**3**) was required. An attempt to obtain **3** by Erlenmeyer's method or by the condensation of 2-substituted 2-oxazolin-5-one (**6**), generated by ethyl chloroformate-mediated cyclisation of **1**, with **2** was unsuccessful. However, isatinimines (**5**), prepared by the inter-

action of isatin (**2**) and primary amines, reacted with **6** to give products which were identical with **4**. This finding confirms that the isothiocyanate-mediated cyclocondensation of **1** with isatins (**2**) generated **6** and **5** which subsequently reacted to give **3** and a free primary amine which in turn brought about aminolysis of the 1,2-bond of the isatin moiety in **3**, followed by ring expansion to 2-oxoquinolines (**4**). The spectral data (IR, PMR) and elemental analyses are in agreement with the proposed structure **4**.

The present method provides a one-pot synthesis of the title compounds, using easily available starting materials. Preparation of these products would be difficult by other routes, particularly because of the functionalities they carry. In view of the importance of quinolines<sup>2,3</sup>, the present findings are potentially useful.

Melting points are uncorrected.

*Reaction of methyl/phenyl isothiocyanate,  $\alpha$ -N-acylglycines (**1**) and isatins (**2**): Formation of N-methyl/phenyl 3-acylamino-2-oxo-1,2-dihydroquinoline-4-carboxamides (**4**)*

Method A: A mixture of **1**, **2** and methyl/phenyl isothiocyanate, taken in the ratio of 1 : 1 : 1.2, was heated for about 30 min in the presence of pyridine as a catalyst. When methyl isothiocyanate was used the temperature was maintained at 130-40°, but it was raised to 140-50° in the case of phenyl isothiocyanate. The reaction mixture was washed successively with pet. ether (40-60°), aq

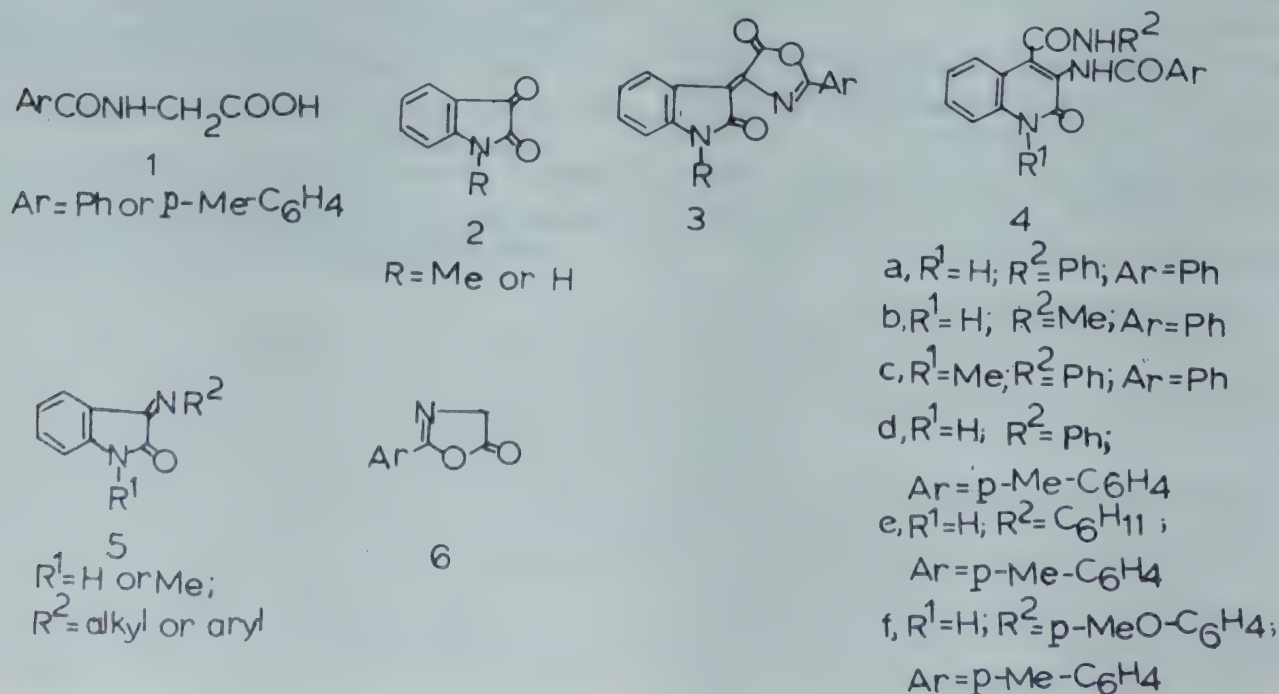


Table 1—Synthesis of N-Substituted 3-Acylamino-2-oxo-1,2-dihydro-4-carboxamides (**4**)

Compd	Method	Yield <sup>a</sup> (%)	m.p. (°C)	Mol. formula	Found (Calc.) %		
					C	H	N
<b>4a</b>	A	37 <sup>b</sup>	273	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	72.0	4.8	11.3
	B	33 <sup>c</sup>			(72.1)	(4.4)	(11.0)
<b>4b</b>	A	29 <sup>b</sup>	238	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·H <sub>2</sub> O	63.7	5.2	12.1
					(63.7)	(5.0)	(12.4)
<b>4c<sup>d</sup></b>	A	36 <sup>b</sup>	245-47	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	72.6	4.4	10.9
	B	25 <sup>c</sup>			(72.6)	(4.8)	(10.6)
<b>4d<sup>e</sup></b>	A	49 <sup>b</sup>	255	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	72.3	5.1	10.3
	B	45 <sup>c</sup>			(72.6)	(4.8)	(10.6)
<b>4e</b>	B	46 <sup>c</sup>	260	C <sub>24</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> ·H <sub>2</sub> O	70.0	6.6	10.4
					(70.0)	(6.3)	(10.2)
<b>4f</b>	B	43 <sup>c</sup>	256	C <sub>25</sub> H <sub>21</sub> N <sub>3</sub> O <sub>4</sub> · $\frac{1}{2}$ H <sub>2</sub> O	68.7	5.2	9.9
					(68.8)	(5.1)	(9.6)

(a) Yields of the pure products are given; (b) yields based on isatin (**2**) taken; (c) yields based on isatinimine (**5**) taken. In this method, **5** was partly recovered during work-up and therefore the actual conversion was higher; (d) PMR(CDCl<sub>3</sub>/TMS):  $\delta$  3.06 (s, 3H, N-CH<sub>3</sub>), 6.49-7.87 (m, 15H, CONH and arom), 9.0 (s, 1H, CONH); (e) PMR(CDCl<sub>3</sub>/TMS):  $\delta$  2.28 (s, 3H, Ar-CH<sub>3</sub>), 6.40-7.75 (m, 14H, CONH and arom), 8.62 (s, 1H, CONH), 8.84 (s, 1H, CONH) ppm.

sodium bicarbonate solution and water. The residue was recrystallised from ethanol. The results are given in Table 1.

*Condensation of 2-aryl-2-oxazolin-5-ones (**6**) with 3-N-alkyl/aryl isatinimines (**5**): Formation of **4***

Method B: To a suspension of N-acyl- $\alpha$ -amino acid (**1**, 1.0 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (1.2 mol), ethyl chloroformate (1.1 mol) was added and the mixture shaken at room temperature until the crystals of the acid dissolved and triethylamine hydrochloride separated out which was filtered off and washed with benzene. The filtrate and washings were combined and to it **5** (1.0 mol) was added

and the mixture heated under reflux for 30 min. After usual work-up the solid residue was recrystallised from ethanol. The relevant data are given in Table 1.

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## Synthesis of *cis*-1-Methyl-2,6-diaryl-4-piperidones

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*cis*-1-Methyl-2,6-diaryl-4-piperidones (**2a-f**), with same or different aryl substituents at C-2 and C-6 of piperidone ring have been synthesised by the addition of methylamine to 1,5-diaryl-1,4-pentadien-3-ones in dimethylformamide. The structures of **2a-f** have been established by elemental analyses and PMR data.

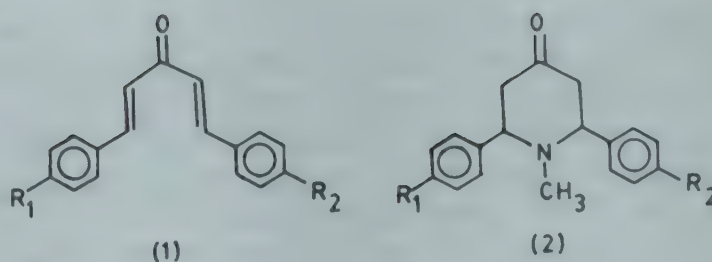
The method commonly employed to synthesise *cis*-1-methyl-2,6-diaryl-4-piperidones (**2**) involves methylation<sup>1</sup> of the corresponding piperidones<sup>2,3</sup>. Condensation of aromatic aldehydes and amines to give **2** has also been reported<sup>4,5</sup>. But these methods suffer from the disadvantage that different aryl groups cannot be introduced at C-2 and C-6 of the piperidone ring. The preparation of **2** by the addition of methylamine to dienones has also been recorded<sup>6,7</sup> but the method appears cumbersome. Herein we report a one pot method for the synthesis of **2**.

*cis*-1-Methyl-2,6-diaryl-4-piperidones (**2**) were prepared in good yields as follows:

Methylamine solution (1 ml, 25-30% w/v) was added slowly to a solution of 1,5-diaryl-1,4-pentadien-3-one (**1**, 0.03 mol) in dimethylformamide (10 ml). The reaction mixture was kept for 24 hr and then poured into crushed ice. The solid separated was filtered, washed with water, dried and crystallised from ethyl alcohol (Table 1).

The formation of piperidones may be envisaged as arising from two consecutive Michael type additions of methylamine to the dienone system.

1,5-Diaryl-1,4-pentadien-3-ones (**1a-d**) with the same aryl groups at C-1 and C-5 were prepared by Claisen-Schmidt condensation according to the method of Conard and Dolliver<sup>8</sup>. The pentadien-3-ones (**1e-i**) with different aryl groups at C-1 and C-5 were obtained by stirring an equimolar mixture of 4-aryl-but-3-en-2-ones<sup>9</sup> and the appropriate aldehyde in ethyl alcohol containing 10% aq. NaOH. After keeping the mixture for 1 hr, yellow crystals separated out.



	R <sub>1</sub>	R <sub>2</sub>
(a)	H	H
(b)	OCH <sub>3</sub>	OCH <sub>3</sub>
(c)	CH <sub>3</sub>	CH <sub>3</sub>
(d)	Cl	Cl
(e)	H	OCH <sub>3</sub>
(f)	OCH <sub>3</sub>	CH <sub>3</sub>

Table 1—Characterisation of *cis*-1-Methyl-2,6-diaryl-4-piperidones (**2**)

Compd	Yield	m.p.* (°C)	Mol. formula	Found (Calc.) %	
				C	H
<b>2a</b>	63	147-49 <sup>1</sup>	C <sub>18</sub> H <sub>19</sub> NO	81.4 (81.5)	7.1 (7.17)
<b>2b</b>	60	129-30	C <sub>20</sub> H <sub>23</sub> NO <sub>3</sub>	73.8 (73.9)	7.0 (7.1)
<b>2c</b>	60	105-7	C <sub>20</sub> H <sub>23</sub> NO	81.8 (81.9)	7.8 (7.9)
<b>2d</b>	35	139-40	C <sub>18</sub> H <sub>17</sub> Cl <sub>2</sub> NO	64.8 (64.7)	5.2 (5.1)
<b>2e</b>	45	108-10	C <sub>19</sub> H <sub>21</sub> NO <sub>2</sub>	77.4 (77.3)	7.2 (7.1)
<b>2f</b>	50	91-93	C <sub>20</sub> H <sub>23</sub> NO <sub>2</sub>	77.5 (77.7)	7.4 (7.4)

\*Melting points are uncorrected.

*cis*-1-Methyl-2,6-diaryl-4-piperidones (**2**) were characterised by elemental analyses and PMR spectra. In the PMR spectra of **2**, the signal due to C-2 and C-6 protons appeared as a doublet of doublet at  $\delta$  3.4  $\pm$  0.05 ( $J$  = 11, 3.5 Hz). The  $J$  values indicate the axial nature of C-2 and C-6 protons thereby suggesting equatorial orientation of the aryl groups at C-2 and C-6; C-3 and C-5 methylene protons appeared as a multiplet in the region  $\delta$  2.40 to 3.00. Thus PMR spectra revealed that the two aryl groups have *cis* relationship with respect to each other. The N-methyl proton appeared at  $\delta$  1.80-1.85. The aromatic protons appeared in the region  $\delta$  6.85 to 7.55.

The 1,4-pentadien-3-ones ( $R_1$  = H,  $R_2$  = CH<sub>3</sub>/Cl and  $R_1$  = OCH<sub>3</sub>,  $R_2$  = Cl) reacted with methylamine to yield unidentified resinous products.

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## Synthesis & Evaluation of N-[2-(Pyridylmethylthio)ethyl]guanidine Analogues as Potential Histamine H<sub>2</sub>-Receptor Antagonists

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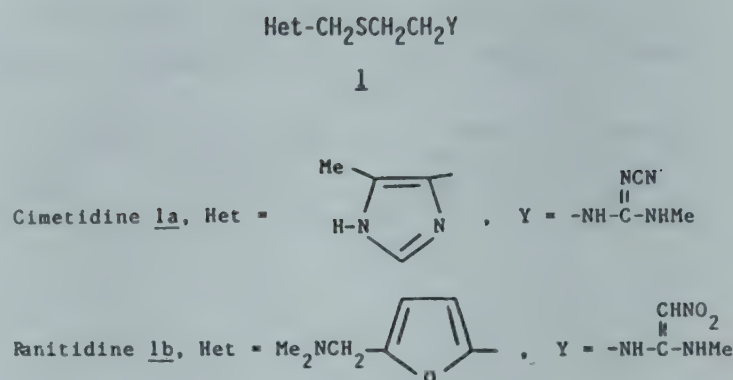
Received 1 January 1987; accepted 23 March 1987

A series of N,N'-dimethoxycarbonyl-N'-[2-(pyridylmethylthio)ethyl]guanidines (**4**) and N-phenyl-N'-[2-(pyridylmethylthio)ethyl]ureas (**7**), thioureas (**8**) and cyanoguanidines (**9**) have been synthesized. The 4-pyridyl analogues **4c** and **8c** are elaborated to the respective 1,2-dihydropyridyl derivatives **5** and **10**. Pharmacological testing using the histamine induced guinea pig atria chronotropic response indicates that compounds **4,5** and **7-10** having terminal N-methoxycarbonyl and N-phenyl substituents, respectively are devoid of histamine H<sub>2</sub>-receptor antagonist activity.

Structure-activity studies for histamine H<sub>2</sub>-receptor antagonists, including the clinically effective cimetidine (**1a**) and ranitidine (**1b**), indicate three common structural features. These include a substituted heterocyclic (Het) ring possessing a basic center linked by a common 2-thiabutyl spacer to a polar hydrogen bonding "urea equivalent" (Y) such as cyanoguanidine or 1-nitro-2,2-diaminoethene as illustrated in **1**<sup>1-3</sup>. Histamine H<sub>2</sub>-receptor antagonists interact with the H<sub>2</sub>-receptor in different ways and activity is dependent upon the nature of the Het moiety and "urea equivalent" (Y).<sup>4</sup>

Previously, we prepared compounds **1** where the Het group was a pyridyl or 1,2-dihydropyridyl ring system and Y was -NHC(=NCN)NHMe and -NHC(=CHNO<sub>2</sub>)N-. The pharmacological test results suggested that the charge distribution in the aromatic pyridyl or 1,2-dihydropyridyl ring was important for interaction with the H<sub>2</sub>-receptor.<sup>5,6</sup> It was, therefore, of interest to determine the effect of incorporation of N,N'-dimethoxycarbonylguanidine and N-phenylurea, thiourea and cyanoguanidine "urea equivalents" (Y) on H<sub>2</sub>-antagonistic activity, and hence the title investigation.

The synthesis of the target N,N'-dimethoxycarbonyl-N'-[2-(pyridylmethylthio)ethyl]guanidines (**4a-**



**c**) and the 1,2-dihydropyridyl analogue (**5**) is outlined in Scheme 1 and the results are summarized in Table 1. Thus, reaction of N,N'-dimethoxycarbonyl-S-methylisothiourea (**2**)<sup>7</sup> with the (2-aminoethylthiomethyl)pyridines (**3a-c**)<sup>5</sup> afforded **4a-c** in 79-81% yield. The sodium borohydride reduction<sup>5,6</sup> of **4c** in the presence of methyl chloroformate in methanol at -65°C led to 4-(1-methoxycarbonyl-1,2-dihydropyridyl) analogue **5** in 68% yield.

Reaction of (2-aminoethylthiomethyl)pyridines (**3a-c**) with phenylisocyanate (**6a**) resulted in the respective N-phenylurea analogues **7a-c** (71-78% yield). Similar reactions of **3a-c** with **6b** led to N-phenylthiourea analogues **8a-c** (74-80% yield). The reaction of **8a-c** with lead cyanamide afforded the corresponding N-phenylcyanoguanidine analogues in 70-74%. Reduction of **8c** with sodium borohydride yielded the 4-(1-methoxycarbonyl-1,2-dihydropyridyl) analogue **10** as outlined in Scheme 2 and summarized in Table 1.

A number of selected compounds were subjected to the chronotropic H<sub>2</sub>-antagonism test using the procedure previously reported.<sup>5</sup>

The N,N'-dimethoxycarbonyl derivatives **4** were prepared to determine the effect which the N,N'-dimethoxycarbonyl substituents had on H<sub>2</sub>-antagonist activity. The 4-pyridyl isomer **4c** was inactive at a concentration of 10<sup>-4</sup> M, probably due to the presence of the terminal methoxycarbonyl substituent as H<sub>2</sub>-antagonists usually possess a terminal N-methyl substituent<sup>1-4</sup> which may be involved in hydrogen-bonding to the H<sub>2</sub>-receptor.<sup>8</sup> The 1,2-dihydropyridyl derivative **5** was similarly inactive. In an earlier study we reported that N-methyl-N'-[2-(pyridylmethylthio)ethyl]thioureas and N'-cyano-N-methyl-N'-[2-(pyridylmethylthio)ethyl]guanidines exhibited H<sub>2</sub>-antagonist activity<sup>5</sup>. The N-phenylurea (**7**), thiourea (**8**) and cyanoguanidine (**9**) analogues were therefore prepared to investigate the effect of replacement of terminal N-methyl sub-

Table 1—Physical Data for N-[2-(Pyridylmethylthio)ethyl]guanidine **4-5**, Urea **7**, Thiourea **8, 10** and Cyanoguanidine **9** Analogues

Compd <sup>a</sup>	Point of attachment <sup>b</sup>	X	Reaction time (hr)	Yield (%)	R <sub>f</sub>	Formula <sup>c</sup>	Exact mass	
							Calc.	Found
<b>4a</b>	C-2	—	3	83	0.70 <sup>d</sup>	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> S	326.1049	326.1049
<b>4b</b>	C-3	—	3	79	0.65 <sup>d</sup>	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> S	326.1049	326.1038
<b>4c</b>	C-4	—	3	81	0.68 <sup>d</sup>	C <sub>13</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub> S	326.1049	326.1041
<b>5</b>	C-4	—	4	68	0.76 <sup>e</sup>	C <sub>15</sub> H <sub>22</sub> N <sub>4</sub> O <sub>6</sub> S	386.1260	386.1251
<b>7a</b>	C-2	O	6	78	0.56 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> OS	287.1093	287.1094
<b>7b</b>	C-3	O	6	71	0.58 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> OS	287.1093	287.1095
<b>7c</b>	C-4	O	6	76	0.60 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> OS	287.1093	287.1101
<b>8a</b>	C-2	S	8	80	0.70 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> S <sub>2</sub>	303.0863	303.0845
<b>8b</b>	C-3	S	8	73	0.72 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> S <sub>2</sub>	303.0863	303.0845
<b>8c</b>	C-4	S	8	79	0.73 <sup>f</sup>	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> S <sub>2</sub>	303.0863	303.0822
<b>9a</b>	C-2	NCN	48	72	0.55 <sup>f</sup>	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> S	311.1205	311.1201
<b>9b</b>	C-3	NCN	48	70	0.59 <sup>f</sup>	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> S	311.1205	311.1208
<b>9c</b>	C-4	NCN	48	74	0.62 <sup>f</sup>	C <sub>16</sub> H <sub>17</sub> N <sub>5</sub> S	311.1205	311.1208
<b>10</b>	C-4	S	4	70	0.73 <sup>g</sup>	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	363.1076	363.1078

<sup>a</sup>Numbers refer to the compounds described in Schemes 1 and 2.

<sup>b</sup>Point of attachment of the pyridinyl or 1,2-dihydropyridinyl ring system.

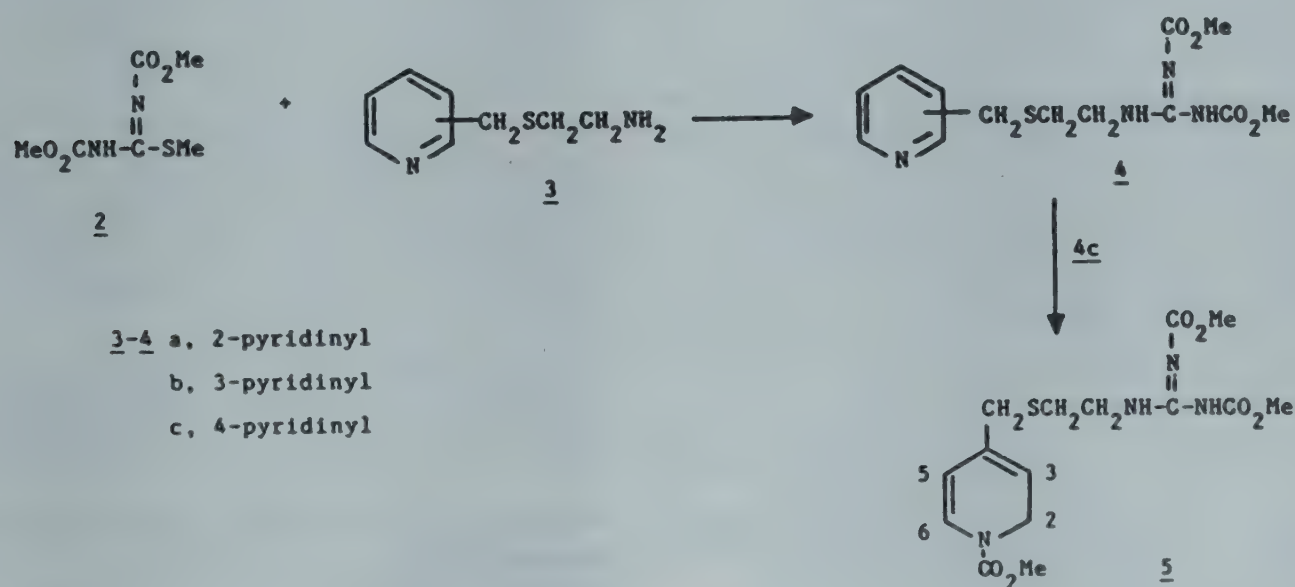
<sup>c</sup>All compounds were isolated as viscous oils.

<sup>d</sup>Dichloromethane:methyl alcohol (9:1 v/v).

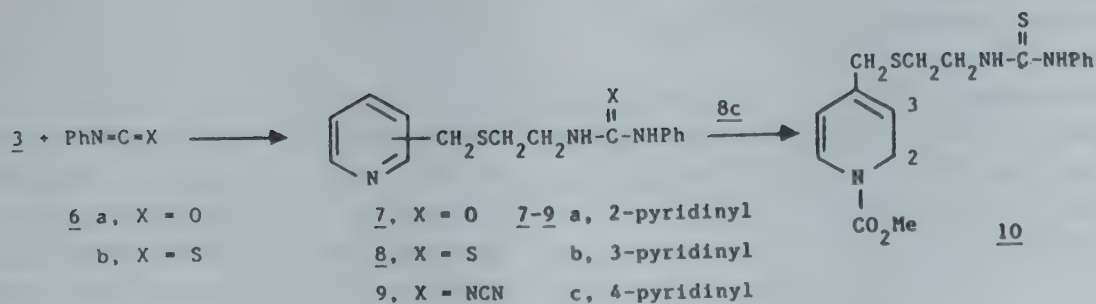
<sup>e</sup>Dichloromethane:methyl alcohol (16:1 v/v).

<sup>f</sup>Chloroform:methyl alcohol (8:1 v/v).

<sup>g</sup>Chloroform:methyl alcohol (16:1 v/v).



Scheme 1



Scheme 2

stituent by a N-phenyl substituent on activity. The observation that the N-phenyl derivatives **7d**, **8d**, **9a**, **9c** and **10** were all devoid of activity indicates that a terminal N-methyl substituent is a requirement for H<sub>2</sub>-antagonist activity.<sup>5</sup>

Nuclear magnetic resonance spectra were recorded in CDCl<sub>3</sub> with TMS as internal standard on a Varian EM-390 or Bruker AM-300 spectrometer, IR spectra (KBr) on a Nicolet 5DX spectrophotometer, mass spectra on an AEI-MS-50 mass spectrometer (exact mass measurements are used in lieu of elemental analyses). Spectral data of only representative compounds of each series are given. The purity of products was ascertained by TLC. Analytical TLC was performed using Whatman PE Sil G/UV 250  $\mu$ m layer silica gel plates and preparative TLC was carried out using Camag DSF-5 silica gel G plates, 1.0 mm in thickness.

*N,N'*-Dimethoxycarbonyl-*N'*-{2-[2-(3- or 4-)pyridylmethylthio]ethyl}guanidines (**4a-c**)

*N,N'*-Dimethoxycarbonyl-S-methylisothiourea (**2**) (3.1 g, 15 mmol)<sup>7</sup> was added to a solution of **3a** (**3b** or **3c**) (15.1 mmol)<sup>5</sup> in methyl alcohol (50 ml) containing a few crystals of *p*-toluenesulfonic acid as catalyst and the reaction mixture was heated at reflux for 3 hr. Removal of the solvent *in vacuo* gave **4a** (**4b** or **4c**) as an oil which was purified on silica gel G plates using dichloromethane-methyl alcohol (9:1, v/v) as development solvent. The product band (see R<sub>f</sub> values listed in Table 1) was extracted with dichloromethane-methyl alcohol (1:1, v/v). Compound **4a**; IR (KBr): 1730 (CO) and 3320 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.74 (*t*, *J* = 7 Hz, 2H, CH<sub>2</sub>N), 3.62 (*t*, *J* = 7 Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 3.72 and 3.8 (two *s*, 3H each, NHCO<sub>2</sub>Me and NCO<sub>2</sub>Me), 3.88 (*s*, 2H, pyridyl-CH<sub>2</sub>S), 7.2 (*d*, *J*<sub>4,5</sub> = 8 Hz of *d*, *J*<sub>5,6</sub> = 5 Hz of *d*, *J*<sub>3,5</sub> = 1.5 Hz, 1H, pyridyl H-5), 7.42 (*d*, *J*<sub>3,4</sub> = 8 Hz, 1H, pyridyl H-3), 7.7 (*d*, *J*<sub>3,4</sub> = 8 Hz of *d*, *J*<sub>4,5</sub> = 8 Hz of *d*, *J*<sub>4,6</sub> = 2 Hz, 1H, pyridyl H-4), 8.54 (*d*, *J*<sub>5,6</sub> = 5 Hz of *d*, *J*<sub>4,6</sub> = 2 Hz, 1H, pyridyl H-6), 8.66 (*bs*, 1H, CH<sub>2</sub>-NH-, exchanges with D<sub>2</sub>O), 9.8 (*bs*, 1H, N HCO<sub>2</sub>Me, exchanges with D<sub>2</sub>O).

*N,N'*-Dimethoxycarbonyl-*N'*-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridylmethylthio)ethyl}guanidine (**5**)

Sodium borohydride (0.14 g, 3.6 mmol) was added to a solution of **4c** (0.293 g, 0.9 mmol) in absolute methyl alcohol (15 ml) precooled in a dry ice-isopropyl alcohol bath. A solution of methyl chloroformate (0.9 mmol) in dry ether (3 ml) was added at a rate such that the temperature of the reaction mixture did not rise above -69°C. The reaction was allowed to proceed with stirring at  $\leq$  -65°C for 4 hr,

poured onto ice-water and sufficient water was added to dissolve the inorganic salts. Extraction with chloroform (3  $\times$  100 ml), washing the combined chloroform extracts with water, drying (MgSO<sub>4</sub>) and removal of the chloroform *in vacuo* gave **5**. The product **5** was purified on silica gel G plates using dichloromethane-methyl alcohol (16:1, v/v). The band containing the product **5** (R<sub>f</sub> 0.76) was extracted with dichloromethane-methyl alcohol (16:1, v/v) to give **5** (0.235 g, 68%) as an oil; IR (KBr): 1720 (CO) and 3320 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.66 (*t*, *J* = 7 Hz, 2H, CH<sub>2</sub>N), 3.13 (*s*, 2H, dihydropyridyl-CH<sub>2</sub>-S), 3.63 (*t*, *J* = 7 Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 3.73 and 3.83 (two *s*, 3H each, NHCO<sub>2</sub>Me and NCO<sub>2</sub>Me), 4.4 (*d*, *J*<sub>gem</sub> = 3 Hz, 2H, dihydropyridyl H-2), 5.0-5.66 (*m*, 2H, dihydropyridyl H-3, H-5), 6.83 (*d*, *J*<sub>5,6</sub> = 6 Hz, 1H, dihydropyridyl H-6), 8.33-9.0 (*m*, 2H, NH protons, exchange with D<sub>2</sub>O).

*N*-Phenyl-*N'*-{2-[2-(3- or 4-)pyridylmethylthio]ethyl}ureas (**7a-c**)

Phenyl isocyanate (2.3 g, 19.3 mmol) was added to a solution of **3a** (**3b** or **3c**) (5.09 g, 30 mmol) in isopropyl alcohol (70 ml) and the reaction mixture was heated at reflux for 6 hr. The solvent was removed *in vacuo*, the residue dissolved in acetone, filtered and the solvent removed *in vacuo* to yield **7a** (**7b** or **7c**), which was purified on silica gel G plates using chloroform-methyl alcohol (8:1, v/v). Extraction of the band having the R<sub>f</sub> value listed in Table 1 with chloroform-methyl alcohol (1:1, v/v) afforded **7**. Compound **7a**; IR (KBr): 1650 (CO) and 3416 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.65 (*t*, *J* = 7 Hz, 2H, CH<sub>2</sub>N), 3.43 (*t*, *J* = 7 Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 3.85 (*s*, 2H, pyridyl-CH<sub>2</sub>S), 5.66-6.3 (*m*, 1H, CH<sub>2</sub>NH, exchanges with D<sub>2</sub>O), 6.73-7.4 (*m*, 8H, NHPh, pyridyl H-3, H-5, NHPh which exchanges with D<sub>2</sub>O), 7.63 (*d*, *J*<sub>3,4</sub> = 8 Hz of *d*, *J*<sub>4,5</sub> = 8 Hz of *d*, *J*<sub>4,6</sub> = 2 Hz, 1H, pyridyl H-4), 8.53 (*d*, *J*<sub>5,6</sub> = 5 Hz of *d*, *J*<sub>4,6</sub> = 2 Hz, 1H, pyridyl H-6).

*N*-Phenyl-*N'*-{2-[2-(3- or 4-)pyridylmethylthio]ethyl}thioureas (**8a-c**)

Phenyl isothiocyanate (2.3 g, 17 mmol) was added to a solution of **3a** (**3b** or **3c**) (5.09 g, 30 mmol) in isopropyl alcohol (70 ml) and the reaction mixture was heated at reflux for 8 hr. The solvent was removed *in vacuo*, the residue dissolved in acetone, filtered and the solvent removed *in vacuo* to yield **8a** (**8b** or **8c**). The products **8** were purified on preparative silica gel G plates, using chloroform-methyl alcohol (8:1, v/v). Extraction of the band having the R<sub>f</sub> values listed in Table 1 with chloroform-methyl alcohol (1:1, v/v) yielded the products **8**. Compound **8a**; IR (KBr): 1090 (CS) and 3320 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.65 (*t*, *J* = 7 Hz, 2H, CH<sub>2</sub>N), 3.43 (*t*, *J* = 7

Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 3.85 (s, 2H, pyridyl-CH<sub>2</sub>-S), 5.66-6.3 (bs, 1H, CH<sub>2</sub>NH, exchanges with D<sub>2</sub>O), 6.73-7.4 (m, 8H, NH Ph, pyridyl H-3, H-5, N HPh which exchanges with D<sub>2</sub>O), 7.63 (d,  $J_{3,4}$  = 8 Hz of d,  $J_{4,5}$  = 8 Hz of d,  $J_{4,6}$  = 2 Hz, 1H, pyridyl H-4), 8.53 (d,  $J_{5,6}$  = 5 Hz of d,  $J_{4,6}$  = 2 Hz, 1H, pyridyl H-6).

*N''-Cyano-N-phenyl-N'-{2-[2-(3- or 4-)pyridylmethylthio]ethyl}guanidines (9a-c)*

Lead cyanamide (2.8 g, 52 mmol) was added to a solution of **8a** (**8b** or **8c**) (6 g, 19.8 mmol) in acetonitrile (260 ml) and dimethylformamide (26 ml) and heated at reflux for 48 hr during which time additional lead cyanamide (7.8 g) was added in aliquots. The solids were filtered and the solvent was removed *in vacuo* to afford **9a** (**9b** or **9c**) which was purified on preparative silica gel G TLC plates using chloroform-methyl alcohol (8:1, v/v). Extraction of the band having the R<sub>f</sub> value listed in Table 1 with chloroform-methyl alcohol (1:1, v/v) afforded **9**. Compound **9a**; IR (KBr): 2168 (CN) and 3350 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.65 (t,  $J$  = 7 Hz, 2H, CH<sub>2</sub>N), 3.43 (t,  $J$  = 7 Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 3.85 (s, 2H, pyridyl-CH<sub>2</sub>-S), 6.0 (br s, 1H, CH<sub>2</sub>NH, exchanges with D<sub>2</sub>O), 7.0-7.4 (m, 8H, NHPh, pyridyl H-3, H-5, N HPh, exchanges with D<sub>2</sub>O), 7.63 (d,  $J_{3,4}$  = 8 Hz of d,  $J_{4,5}$  = 8 Hz of d,  $J_{4,6}$  = 2 Hz, 1H, pyridyl H-4), 8.53 (d,  $J_{5,6}$  = 5 Hz of d,  $J_{4,6}$  = 2 Hz, 1H, pyridyl H-6).

*N-Phenyl-N'-{2-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)methylthio]ethyl}thiourea (10)*

Sodium borohydride (0.23 g, 6 mmol) was added to a solution of **9c** (0.606 g, 2 mmol) in absolute methyl alcohol (10 ml) precooled in a dry ice-isopropyl alcohol bath. A solution of methyl chloroformate (0.189 g, 2 mmol) in dry ether (3 ml) was added dropwise at -69°C. The reaction was allowed to proceed with stirring at -69°C for 4 hr, after which the reaction mixture was allowed to return to 25°C. The reaction mixture was poured onto ice-water and enough water was added to dissolve the inorganic salts. Extraction with chloroform (4 × 100 ml),

washing the combined extracts with water, drying (MgSO<sub>4</sub>) and removal of the chloroform *in vacuo* yielded **10**, which was purified on preparative silica gel G plates using chloroform-methyl alcohol (16:1, v/v). Extraction of the band (R<sub>f</sub> 0.73) afforded **10** (0.508 g, 70%) as an oil; IR (KBr): 1090 (CS) and 3320 (NH) cm<sup>-1</sup>; PMR:  $\delta$  2.7 (t,  $J$  = 7 Hz, 2H, CH<sub>2</sub>N), 3.12 (s, 2H, dihydropyridyl-CH<sub>2</sub>-S), 3.75 (s, 3H, OMe), 3.9 (t,  $J$  = 7 Hz, 2H, SCH<sub>2</sub>CH<sub>2</sub>N), 4.37 (d,  $J_{gem}$  = 3 Hz, 2H, dihydropyridyl H-2), 5.1 (m, 1H, dihydropyridyl H-5), 5.4 (m, 1H, dihydropyridyl H-3), 6.5 (br s, 1H, CH<sub>2</sub>NH, exchanges with D<sub>2</sub>O), 6.75 (d,  $J_{5,6}$  = 6 Hz, 1H, dihydropyridyl H-6), 7.17-7.62 (m, 5H, Ph), 8.07 (bs, 1H, N HPh, exchanges with D<sub>2</sub>O).

We are grateful to the Medical Research Council of Canada Grants (MT-4888 and MT-4792) for financial support of this work. We also thank the Alberta Heritage Foundation for Medical Research for a studentship to one of us (O.M.E.).

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### Corrigendum

Paper entitled, "Synthesis of naturally occurring pratensein & 6,8-di-C-prenylpratensein", *Indian J Chem*, **26B** (1987) 488-490.

According to the authors the  $^{13}\text{C}$  NMR data for compound **4a** (p.489) reported by them was wrong. The correct data now provided by the authors is reproduced below:

50 MHz  $^{13}\text{C}$ -NMR ( $\text{CD}_3\text{COCD}_3$ ): 55.24 (q,  $\text{OCH}_3$ ), 93.46 (d, C-8), 98.93 (d, C-6), 106.40 (s, C-10), 111.41 (d, C-5'), 116.08 (d, C-2'), 119.90 (d, C-6'), 122.71 (s, C-1'), 123.74 (s, C-3), 146.30 (s, C-3'), 147.64 (s, C-4'), 153.4 (d, C-2), 157.86 (s, C-9), 162.66 (s, C-5), 164.55 (s, C-7) and 180.42 (s, CO).

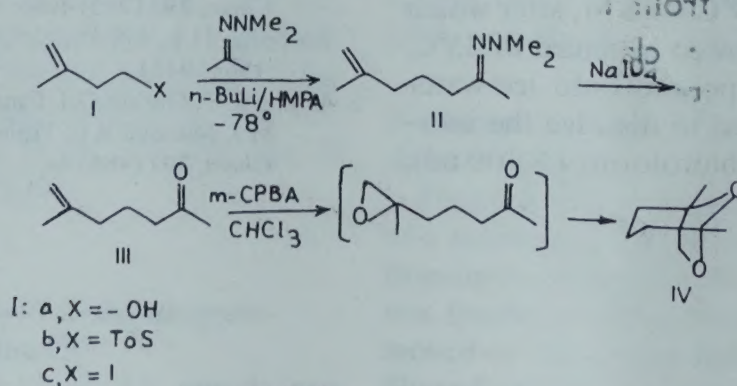
### Errata

Paper entitled, "Synthesis of some 3-phenoxybenzyl 2,2-dihalocyclopropyl ethers", *Indian J Chem*, **26B** (1987) 445-447.

On p. 446 (para 2, line 2) there is a misprint in the dose of compound V required for 100% mortality against adult *Musca domestica*. The second line "adult *Musca domestica* at a dose of 5 g/insect" should read as "adult *Musca domestica* at a dose of 5  $\mu\text{g}$ /insect".

Paper entitled "A new synthesis of ( $\pm$ )-frontalin, the pheromone of *Dendroctonus* bark beetles", *Indian J Chem*, **25B** (1986) 1243-1244.

Through oversight wrong Scheme 1 has been printed on p. 1243. The correct Scheme 1 is as printed below:



SCHEME 1

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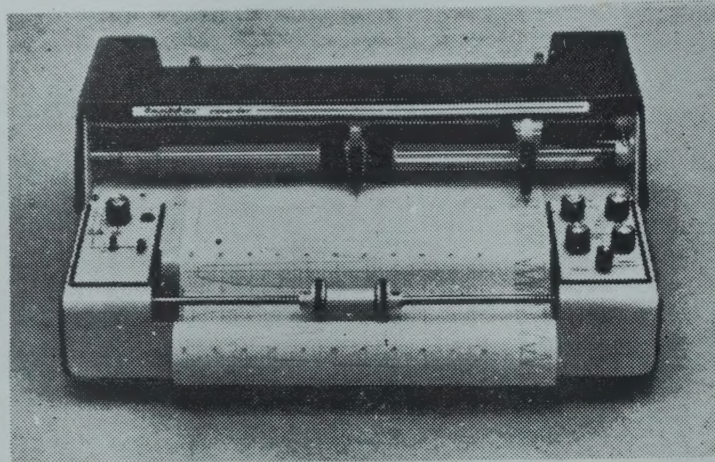
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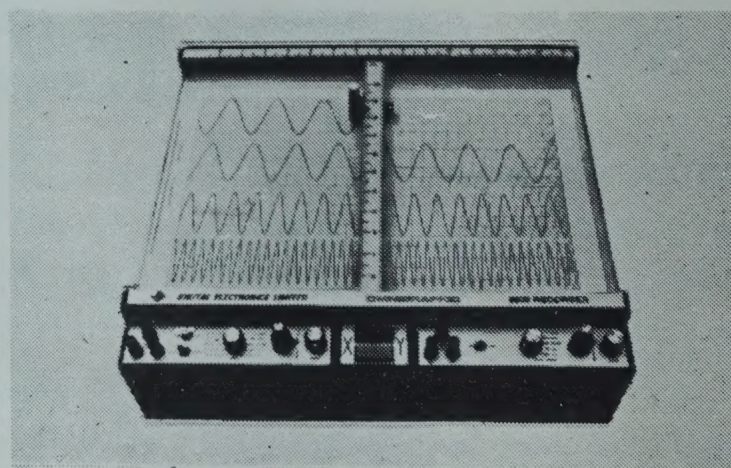
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The series 5000 Strip Chart Recorder and the series 2000 XY Recorder are well proven instruments incorporating State of the Art Circuitry. A wide range of models offer tremendous flexibility to the user. With over 5000 installations, these instruments are the preferred choice of discriminating users all over India.

## Series 2000 XY Recorder



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